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Award Number: W81XWH-08-1-0725

TITLE: Investigation of Prognostic Ability of Novel Imaging Markers for Traumatic Brain Injury (TBI)

PRINCIPAL INVESTIGATOR: Rao P Gullapalli

CONTRACTING ORGANIZATION: University of Maryland  
Baltimore, MD 21201

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Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES					
14. ABSTRACT This is the third annual report for the award made on September 15, 2008. Since the last report the above study has recruited 72 patients. Thirty six of these patients completed their one month scan, 25 completed their 6 month scan and 2 completed their 18 month scan. Since the last annual report, the IRB protocol went through additional modifications, mainly to streamline the process of recruitment of moderate and severe patients into the study. Currently we have screened over 300 patients that have been admitted to the Shock Trauma Center. At this point the recruitment process is smooth although there are some challenges in the recruitment of the severe patients within the first 10 days of injury. Several presentations were made at international meetings mainly on the resting state data which clearly show a decrease in the default mode network among the mildly injured patients that seem to take as long as 6 months to recover to the control levels. A manuscript of retrospective analysis of severely injured TBI patients to determine whether DTI parameters would be predictive of their outcomes has now led to a full manuscript which is being submitted to the Journal of Neurotrauma injured patients					
15. SUBJECT TERMS Traumatic Brain Injury, diffusion tensor imaging, ANAM, spectroscopy					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT  UU	18. NUMBER OF PAGES  176	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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## **Introduction**

The goal of this study is to identify advanced magnetic resonance imaging markers that can serve as a prognostic marker in the evaluation and management of traumatic brain injury patients. This study will recruit 120 patients with varying severity of traumatic brain injury (mild, moderate, severe) with an initial diagnosis of diffuse axonal injury. Neuropsychological testing and magnetic resonance imaging will be performed in the acute (less than 5 days following injury), and recovery stages (4 weeks, 6 months, and 18 months). The relationship between the advanced magnetic resonance imaging markers and the clinical condition of the patient will be evaluated at each time point to determine which of the imaging markers, or a combination of imaging markers are best representative of the clinical condition of the patient. Further, the markers will be evaluated for their prognostic ability to determine the clinical course of the TBI patients.

## **Key Research Accomplishments**

Most of last year was spent focusing on recruitment. A steady growth in recruitment was achieved thanks to the effort of the research staff. A total of 72 patients received their first scan, 36 completed their one month scan, 25 completed their 6 month scans and 2 completed their 18 month scans.

Currently we have screened over 300 patients that have been admitted to the Shock Trauma Center. Although improved, moderate and severe injury patients continue to be a problem for recruitment. The moderate are mostly a problem because very few patients are actually classified as moderate. Severely injured patients were a problem in the beginning because of research related transportation of sick subjects to the MRI. But towards the later part of the year this has been resolved and the nursing staff has been now trained to transport research patients.

## **Reportable Outcomes:**

We have been focused on the analysis of resting state functional MRI data. Our initial data suggests that functional connectivity within the default mode network (DMN) is disrupted initially following mild TBI with decreased functional connectivity in the bilateral frontal cortex, right medial temporal lobe (MTL), and bilateral thalamus. This disruption appears to normalize at one month with the functional connectivity approaching that of the controls in the thalamus, right MTL, left frontal but still showing decreased functional connectivity within the right frontal cortex. The frontal cortex is involved in executive function and working memory which are common reported deficits of mild TBI. We believe that this longitudinal analysis of functional connectivity within the resting state helps to explain some of the cognitive deficits associated with mild TBI that persist for over one month after the initial injury. This work was presented at the International Society for Magnetic Resonance in Medicine in Montreal, the abstract for which is attached in the appendix.

To objectively assess the stability of the resting state networks we focused on the reliability of motor resting state network on healthy volunteers as several of the mild injury patients have reported balance problems on their Rivermead questionnaire. Resting state functional connectivity of the cortical motor network has been shown to be reliable and consistent; however, the same has not been shown for measurements of effective connectivity. We used structural equation modeling (SEM), a frequently used method to evaluate effective connectivity, to evaluate reliability of these measurements in the human resting state motor network. Because connectivity measurements have shown sensitivity to physiological noise, we performed our reliability assessment using four different filtering methods. The filtering methods used were i) Standard preprocessing with no physiological filtering ii) retrospective correction of physiological effects using RETROICOR (a physiologically based filter) iii) White matter + CSF mean signal filtering and iv) whole brain mean signal filtered



data. Exploratory SEM analysis was performed to obtain a causal model for effective connectivity using the 1dSEM tool in AFNI. Anatomical constraints were used to prevent SEM from yielding models that fit the data well, but with paths that are not anatomically feasible. For example, contralateral connections from the primary motor area to the premotor area were excluded. The resulting resting state motor network has reciprocal connections between the supplementary motor area and the bilateral primary and pre-motor areas. The resulting model follows a hierarchical structure with the premotor areas influencing the ipsilateral and contralateral primary motor areas, and the left primary influencing the right primary motor area. Overall the path coefficients demonstrated high degree of variability. The variability of both functional connectivity and effective connectivity was less for the physiologically filtered dataset and the dataset with no filtering, compared to the WM-CSF and global mean filtered datasets. Given the variability of effective connectivity from SEM, interpretation of such data should be treated with caution and should be taken into account when dealing with data from patients following TBI. Work from this study was submitted to NeuroImage which was reviewed and came back with some good critiques and suggestions. We are in the process of addressing these critiques and will resubmit the paper once everything is addressed to our satisfaction. Results from this study were also presented at the International Society for Magnetic Resonance in Medicine (abstract attached in appendix).

Analysis of the retrospective data from severe TBI patients to determine whether DTI parameters from these patients would be predictive of their outcomes was completed and submitted to Lancet. Unfortunately the manuscript was rejected and we are now in the process of repackaging the manuscript for submission to the Journal of Neurotrauma. In this study, the relationship of DTI measures including apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial ( $\lambda_{||}$ ), and radial diffusivity ( $\lambda_{\perp}$ ) from the whole brain white matter, internal capsule, genu, splenium, and body of the corpus callosum were compared with neurological status at MRI and at discharge to acute TBI rehabilitation. Whole brain white matter averages of ADC,  $\lambda_{||}$ , and  $\lambda_{\perp}$  and their coefficient of variation (CV) were significantly correlated with the Glasgow Coma Scale (GCS) on the day of MRI. The average  $\lambda_{||}$  was significantly correlated with GCS on the day of MRI in all measured brain regions. Outcomes were associated with whole brain white matter averages of ADC and  $\lambda_{||}$  and the CVs of FA, ADC,  $\lambda_{||}$ , and  $\lambda_{\perp}$ ; and the averages and CVs of FA and  $\lambda_{||}$  in all corpus callosum regions. The inclusion of regional and global DTI measures improved the accuracy of prognostic models, when adjusted for admission GCS and age ( $p < 0.05$ ). Whole brain white matter and regional DTI measures are sensitive markers of TBI and correlate with neurological status both at MRI and discharge to rehabilitation. The addition of DTI measures adjusted for age, gender, and admission GCS significantly improved prognostic models. These results are encouraging and it remains to be seen whether this relationship holds in the prospective study for the three groups of patients (mild, moderate, and severe). A copy of the working manuscript is attached.

## Conclusion

This last year, recruitment of patients into the study has steadily grown. The group meets on a weekly basis with the goals of identifying issues related to recruitment and every case is discussed at these meetings. At this weekly meeting various aspects of the data including quality are discussed. We continue to keep in constant contact with the Trauma physicians, recruitment team, and the neurosurgeons all working towards the goal of increased recruitment and retainment. Dr. Larry Latour is now one of the Ph.D. dissertation committee members for Chandler Sours who is a graduate student helping with this study. We continue to explore the possibility of sharing patients and possibly even extending the study to other population including high school athletes.

Data analysis will continue both on the imaging side and also on the neurocognitive end. We have made several presentations at various conferences and were invited to two special conferences

on TBI. We have also asked for a no cost extension for the study. Because of regulatory and other reasons our study started about a year after the award was made. We hope to obtain the no cost extension soon which will allow us to complete the recruitment of the desired patients. We will continue to work on data analysis and prepare manuscripts on a constant basis

## References

1. **Sours, C.**, Betz, J., Roys, S., Aarabi, B., Shanmuganathan, K., Greenspan, J., Gullapalli, R. Disruption of Default Mode Network following Mild Traumatic Brain Injury. Proceedings of 2011 Annual Meeting International Society for Magnetic Resonance in Medicine. Palais des congrès de Montréal, Québec, Canada. May 7-13, 2011.
2. **Sours, C.**, Betz, J., Roys, S., Aarabi, B., Shanmuganathan, K., Greenspan, J., Gullapalli, R. Disruption of the Functional Connectivity Following Mild Traumatic Brain Injury. Proceedings of 2011 Annual Meeting of the Organization of Human Brain Mapping. Centre des Congrès de Québec, Québec City, Canada. June 26-30, 2011.
3. Kavallappa T, Roys S, Roy A, Greenspan J, Gullapalli R, McMillan A. Reliability of functional and effective connectivity of the resting state motor network in healthy subjects. Proceedings of the 2011 Annual Meeting of the International Society for Magnetic Resonance in Medicine, Palais des congrès de Montreal, Quebec, Canada.
4. Betz J, Zhuo J, Roy A, Shanmuganathan K, Gullapalli RP., Prognostic value of diffusion tensor imaging parameters in severe traumatic brain injury. Manuscript submitted to Lancet but being revised for J of Neurotrauma.

## Appendices

1. Protocol for the Study
2. Abstract presentation on 'Disruption of Default Mode Network following Mild Traumatic Brain Injury', at the ISMRM, Montreal 2011
3. Abstract presentation on 'Disruption of Functional Connectivity Following Mild Traumatic Brain Injury, at the Organization for Human Brain Mapping Meeting 2011, Quebec City, Quebec, Canada.
4. Copy of presentation made at the CDMRP Cures Conference in Virginia, Feb 2011.
5. Copy of invited Presentation made at the Biological Assessment of Brain Dysfunction conducted by DVBIC in May 2011.
6. Manuscript that was submitted to Lancet, now being reworked for J of Neurotrauma.



Date: Tuesday, May 03, 2011 6:29:14 AM

View: Introduction Page

Print Close



## Introduction Page

- 1 \* **Abbreviated Title:**  
Imaging of Traumatic Brain Injury
- 2 \* **Full Title:**  
Prognostic value of MR Imaging Markers in the Assessment of Traumatic Brain Injury Patients
- 3 \* **Select Type of Submission :**  
New IRB Application
- 4 **Original Version #:**

ID: VIEW439861A002800  
Name: Introduction Page

View: Type of Application



## Type of Application

- 1 \* **Select the most appropriate answer:**
  - ☐ I have an existing external sponsor's protocol.
  - ☒ I do not have an existing external sponsor's protocol.

ID: VIEW4572037F13C00  
Name: Type of Application

View: NIH Sponsored Study

## NIH Sponsored Study

- 1 \* **Is this a National Institutes of Health (NIH) sponsored study?**
  - ☐ Yes
  - ☒ No

ID: VIEW45869AB314800  
Name: NIH Sponsored Study

View: Research Team Information



## Research Team Information

- 1 **\* Principal Investigator** - Who is the PI for this study (person must have faculty PI status)?

Rao Gullapalli

- 2 **Point of Contact** - Who is the alternative point of contact for the PI? (If **not** Principal Investigator). This person can be a study coordinator or any other study team member. In case the IRB can not contact the PI, this person is a secondary person to contact:

Kiscia Cannon

- 3 **Other Team Members** - list all additional members of the research team for this study. DO NOT include the PI or POC in this list:

Name	Edit Submission	CC on Email	Research Role
Michael J. Makley	no	yes	Sub-Investigator
Bizhan Aarabi	no	yes	Sub-Investigator
Chandler Sours	yes	yes	Study Coordinator
Amechi Anazodo	no	no	Research Team Member
Alyse Gettings	no	no	Research Team Member
Diane Rouse	no	no	Research Team Member
Robert Kane	no	no	Sub-Investigator
Bonnie McManus	no	no	Technician or Assistant
Deborah Stein	no	no	Research Team Member
Allison Lindell	no	no	Research Team Member
Jonathan Gooch	no	yes	Research Team Member
Daniel Mayer	no	no	Research Team Member
Keri Volpini	no	no	Research Team Member
Emily Cooper	no	no	Technician or Assistant
Alison Cernich	no	no	Research Team Member
Tondeleyo C. Gonzalez	no	no	Research Team Member
Jiachen Zhuo	yes	yes	Research Team Member
Joshua Betz	yes	yes	Research Team Member
Genna Stephanie McFarland	no	no	Research Team Member
Olga Kolesnik	no	no	Research Team Member
Marianne Hattan	no	no	Research Team Member
Steven Roys	no	yes	Research Team Member
Sean Crane	no	no	Research Team Member

Name	Edit Submission	CC on Email	Research Role
Margaret Mensa	no	no	Research Team Member
Jacqueline Janowich	yes	yes	Study Coordinator
Kathirkamnathan Shanmuganathan	no	yes	Sub-Investigator
Danielle Lynn Stern Stegman	no	no	Research Team Member
Kevin Sheth	no	no	Research Team Member
Yawei Wang	no	no	Research Team Member
Kim Taylor	no	no	Study Coordinator
Sarah Wade	no	no	Research Team Member
Jamila Torain	no	no	Research Team Member
Anindya Roy	no	yes	Statistician
Christine Wade	no	no	Research Team Member

**IMPORTANT NOTE:** All Research Team Members must log into CICERO and complete the Conflict of Interest Statement in the **Submit COI Statement** activity. All research team members' COI statements MUST BE COMPLETED before the application can be submitted.

ID: VIEW4398738E5FC00  
Name: Research Team Information

View: Sites Where Research Activities Will Be Conducted

## Sites Where Research Activities Will Be Conducted

- \* Is this study a:**

☐ Single Site

☒ Multi-Site
- \* Is UMB the Coordinating Center for this study?**

☒ Yes ☐ No
- \* Institution(s) where the research activities will be performed:**

University of Maryland Medical Center

UMB School of Medicine

Shock Trauma Center

Kernan Hospital

ID: VIEW44034A9C4E800  
Name: Sites Where Research Activities  
Will Be Conducted

View: Initiating Research

## Initiating Research

- 1 \* [Indicate who is initiating this research:](#)  
Federal

ID: VIEW457208B0A2800  
Name: Initiating Research

[View: Funding Information](#)

## Funding Information

- 1 \* [Indicate who is funding the study](#)  
Federal
- 2 \* [What portion of the research is being funded?](#)  
Procedures  
Staff  
Participant Compensation
- 3 [Please discuss any additional information regarding funding below:](#)

ID: VIEW44034B7AE7000  
Name: Funding Information

[View: Federal Agency Sponsor Information](#)

## Federal Agency Sponsor Contact Information

- \* [Agency Name:](#)  
USA MED RESEARCH AND MATERIEL COMMAND - DEPARTMENT OF DEFENSE
- \* [Address 1:](#)  
1077 PATCHEL STREET
- [Address 2:](#)
- \* [City:](#)  
FORT DETRICK
- \* [State:](#)  
MD

\* Zip Code:

21702

\* Contact Person:

AYI AYAYI

\* Phone Number:

301-619-4018

Grant Number 1 (if applicable):

- OR - Check here if Grant 1 is not assigned a number. ☐

If Grant 1 has no number, please provide the following information:

Title of Grant 1:

PI of Grant 1:

Grant Number 2 (if applicable):

- OR - Check here if Grant 2 is not assigned a number. ☐

If Grant 2 has no number, please provide the following information:

Title of Grant 2:

PI of Grant 2:

Grant Number 3 (if applicable):

- OR - Check here if Grant 3 is not assigned a number ☐

If Grant 3 has no number, please provide the following information:

Title of Grant 3:

PI of Grant 3:

Grant Number 4 (if applicable):

- OR - Check here if Grant 4 is not assigned a number. ☐

If Grant 4 has no number, please provide the following information:

Title of Grant 4:

PI of Grant 4:

ID: VIEW4573786F8C800  
Name: Federal Agency Sponsor  
Information

View: Organization Review Requirements



## Organization Review Requirements (other than IRB)

Answer the following questions to determine additional organizational review requirements:

- 1 **Department/Division Review** - All research submissions are required to undergo department/division/institutional review prior to IRB review. The following entity is listed as the required department/division/institutional review:

***Diagnostic Radiology***

If this information is incorrect, please notify the HRPO office.

- 2 **RSC Review Criteria** - Answer the following questions to determine if review by the Radiation Safety Committee may be required:

\* 2.1 - Does the research involve the use of ionizing radiation? See "Help" for definitions, examples, and additional information. ☐ Yes ☒ No

\* 2.2 - Does the research involve the sampling of radioactive human materials for subsequent use or analysis in a laboratory? ☐ Yes ☒ No

- 3 **IBC Review Criteria** - Answer the following questions to determine if review by the Institutional Biosafety Committee may be required. See "Help" for definitions, examples, and other information:

3.1 - Does the research involve human gene transfer ☐ Yes ☒ No

**OR**

\* Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.

\* 3.2 - Does the research involve: a) the exposure of human subjects to pathogenic microorganisms, or b) the potential exposure of UMB research staff to infectious materials through the sampling or processing of materials from patients with known infectious disease or from environmental surfaces? ☐ Yes ☒ No



3.3 - Does the research involve the sampling of materials from persons with no known  
 \* infectious disease and where the only risk to study staff is occupational exposure to  
 bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard? ☐ Yes ☒ No

4 **Cancer Center Criteria** - Answer the following to determine if review by the Cancer Center (Hematology-Oncology) may be required:

\* Does the protocol involve in any way studies related to the prevention, treatment,  
 diagnosis, or imaging of neoplastic diseases? ☐ Yes ☒ No

5 **General Clinical Research Center Review Criteria** - the GCRC offers free and/or cost shared resources for patient oriented research.  
[Click Here for more information.](#)

Answer the following to determine if review by the GCRC may be required:

\* Will the General Clinical Research Center (GCRC) facility or resources be used to conduct  
 this activity?: ☐ Yes ☒ No

6 **VA Review Criteria** - Answer the following questions to determine if review by the VAMHCS R&D Committee may be required:

6.1 - Will the research be conducted completely or partially in VA facilities or at VA  
 \* approved off-site locations/facilities (including VA-leased space) or otherwise utilizes VA  
 resources? ☐ Yes ☒ No

\* 6.2 -Will the research be conducted by researchers with VA appointments while on official  
 VA duty (including those with WOC status)? ☐ Yes ☒ No

\* 6.3 - Will the VAMHCS or its satellites will be recruitment sites for this research project? ☐ Yes ☒ No

\* 6.4 - Is the research VA-funded? ☐ Yes ☒ No

\* 6.5 - Does the research involve VA medical records or VA databases, or otherwise derives  
 data from intervention or interaction with VAMHCS subjects or tissues? ☐ Yes ☒ No

7 **Conflict of Interest (COI)** - IRB policies require that each and every member of the study team must declare any conflicts of interest for  
 this Application submission. This means that each member of the study team must independently log into this site and execute the "Submit  
 COI Statement" activity. The study team members and the status of their COI declaration for this submission appears below:

Researcher	COI Statement Submitted	Date Submitted	CISC Review Date
Rao Gullapalli	Yes	1/19/2009	Not Reviewed by CISC
Kiscia Cannon	No	Not Submitted Yet	N/A
Christine Wade	Yes	7/28/2009	Not Reviewed by CISC
Kim Taylor	Yes	12/7/2009	Not Reviewed by CISC
Daniel Mayer	Yes	8/30/2010	Not Reviewed by CISC
Keri Volpini	Yes	7/28/2009	Not Reviewed by CISC
Jamila Torain	Yes	3/3/2011	Not Reviewed by CISC
Michael J. Makley	Yes	1/30/2009	Not Reviewed by CISC
Jiachen Zhuo	Yes	1/20/2009	Not Reviewed by CISC

Researcher	COI Statement Submitted	Date Submitted	CISC Review Date
Jacqueline Janowich	Yes	11/8/2010	Not Reviewed by CISC
Kathirkamnathan Shanmuganathan	Yes	1/29/2009	Not Reviewed by CISC
Amechi Anazodo	Yes	11/30/2009	Not Reviewed by CISC
Anindya Roy	Yes	2/2/2009	Not Reviewed by CISC
Sean Crane	Yes	11/9/2010	Not Reviewed by CISC
Bonnie McManus	Yes	2/22/2011	Not Reviewed by CISC
Bizhan Aarabi	Yes	2/8/2009	Not Reviewed by CISC
Margaret Mensa	Yes	8/1/2009	Not Reviewed by CISC
Robert Kane	Yes	8/5/2009	Not Reviewed by CISC
Yawei Wang	Yes	7/29/2009	Not Reviewed by CISC
Danielle Lynn Stern Stegman	Yes	7/28/2009	Not Reviewed by CISC
Genna Stephanie McFarland	Yes	7/28/2009	Not Reviewed by CISC
Olga Kolesnik	Yes	8/15/2009	Not Reviewed by CISC
Emily Cooper	Yes	2/24/2011	Not Reviewed by CISC
Marianne Hattan	Yes	7/31/2009	Not Reviewed by CISC
Sarah Wade	Yes	7/28/2009	Not Reviewed by CISC
Joshua Betz	Yes	10/1/2009	Not Reviewed by CISC
Jonathan Gooch	Yes	7/28/2009	Not Reviewed by CISC
Alison Cernich	Yes	8/3/2009	Not Reviewed by CISC
Diane Rouse	Yes	4/21/2010	Not Reviewed by CISC
Steven Roys	Yes	1/20/2009	Not Reviewed by CISC
Alyse Gettings	Yes	8/27/2010	Not Reviewed by CISC
Kevin Sheth	Yes	4/21/2010	Not Reviewed by CISC
Chandler Sours	Yes	8/24/2010	Not Reviewed by CISC
Tondeleyo C. Gonzalez	Yes	7/28/2009	Not Reviewed by CISC
Deborah Stein	Yes	10/1/2009	Not Reviewed by CISC
Allison Lindell	Yes	7/28/2009	Not Reviewed by CISC

8 **Department of Health and Mental Hygiene (DHMH)** - Answer the following questions to determine whether or not DHMH review is needed:

\* 8.1 DHMH will rely on UMB IRB for review of this protocol? ☒ Yes ☐ No

\* 8.2 This protocol will need DHMH IRB review? ☐ Yes ☒ No

ID: VIEW44034C719B400  
Name: Organization Review  
Requirements

View: Summary of Required Reviews

## Summary of Required Reviews (other than IRB)

1 **Additional Committee Reviews** - Based on your responses to the previous questions, you have identified the following additional reviews. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's webpage.

Name of Related Submission

*This protocol has no related submissions (RSC, GCRC, IBC, etc)*

- 2 Required Department and Specialty Reviews** - Based on the PI's organization (department, division, etc.) affiliation and answers to previous questions (use of Cancer Center, etc.), the organizations listed below are required to review this application. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	Review Status
Diagnostic Radiology	Complete

ID: VIEW440367DB65800  
Name: Summary of Required Reviews

View: Risk Level



## Risk

**\* Choose One:**

- ☒ Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.
- ☐ Greater Than Minimal - Does not meet the definition of Minimal Risk.

ID: VIEW43BD8D9C46C00  
Name: Risk Level

View: Exempt\_Determination

## Exempt Determination

- 1 Choose ONE or MORE Exempt Categories from the list below. If your study meets NONE of the below listed criteria, leave the answers BLANK, and click the Continue button:**

- ☐ **45 CFR 46.101(1)** Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- ☐ **45 CFR 46.101(2)** Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

- ☐ **45 CFR 46.101(3)** Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

- ☐ **45 CFR 46.101(4)** Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. PLEASE NOTE: According to the Office for Human Research Protections (OHRP), to qualify for this exemption the data, documents, records, or specimens must be in existence before the project begins. The principle behind this policy is that the rights of individuals should be respected; subjects must consent to participation in research.

- ☐ **45 CFR 46.101(5)** Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

- ☐ **45 CFR 46.101(6)** Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

ID: VIEW48675960F0C01  
Name: Exempt\_Determination

View: Expedited\_Determination

## Expedited Determination

- 1 **Choose ONE ore MORE Expedited Category from the list below. If your study meets NONE of the below listed criteria, leave the answers BLANK, and click the Continue button:**

- ☐ **45 CFR 46.110 (1)(a)** Clinical studies of drugs and medical devices when research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
- ☐ **45 CFR 46.110 (1)(b)** Clinical studies of drugs and medical devices when research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- ☐ **45 CFR 46.110 (2)(a)** Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week.

- ☐ **45 CFR 46.110 (2)(b)** Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

- ☐ **45 CFR 46.110 (3)** Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

- ☒ **45 CFR 46.110 (4)** Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

- ☐ **45 CFR 46.110 (5)** Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

- ☐ **45 CFR 46.110 (6)** Collection of data from voice, video, digital, or image recordings made for research purposes.

- ☒ **45 CFR 46.110 (7)** Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

- ☐ **45 CFR 46.110 (8)(a)** Continuing review of research previously approved by the convened IRB as follows: (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects.

- ☐ **45 CFR 46.110 (8)(b)** Continuing review of research previously approved by the convened IRB as follows: (b) where no subjects have been enrolled and no additional risks have been identified.

- ☐ **45 CFR 46.110 (8)(c)** Continuing review of research previously approved by the convened IRB as follows: (c) where the remaining research activities are limited to data analysis.

- ☐ **45 CFR 46.110 (9)** Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

ID: VIEW48675A98D4000  
Name: Expedited\_Determination

View: Qualifies As Expedited

**Based on the information you have provided, your study may qualify for EXPEDITED REVIEW. Click on the CONTINUE button below to complete the rest of the submission.**

ID: VIEW43CBE29BE1800  
Name: Qualifies As Expedited

View: Waiver of Consent

## Waiver of Consent

- 1 \* Will this research require a waiver of consent?

☐ Yes ☒ No

ID: VIEW43B3982218000  
Name: Waiver of Consent

View: Type of Research

## Type of Research

- 1 \* Indicate the type of research this study involves (Choose all applicable):

- ☐ Device  
☐ One or more drugs or biologics

- ☐ Genetics testing
- ☐ None of the above
- ☒ Psychological / Sociological

ID: VIEW4514342955C00

Name: Type of Research

View: Lay Summary

## Lay Summary

- 1 **\* Provide a summary of the background and purpose of the study in *lay terms*. This summary will be used during the IRB review and should include layman's terms and language that can be understood by a person without a medical degree.**

The goal of this study is to identify advanced magnetic resonance imaging markers that can serve as a prognostic marker in the evaluation and management of traumatic brain injury patients. This study will recruit traumatic brain injury patients whose injuries vary from mild to severe.

Magnetic resonance imaging and cognitive testing (when possible) will be performed in the acute (within 10 days following injury), and recovery stages (about 1 month, about 6 months, and about 18 months). The relationship between the advanced magnetic resonance imaging markers and the clinical condition of the patient will be evaluated at each time point to determine which combination of imaging markers best describe the current clinical status of the patient and which markers best predict a patient's outcome status.

ID: VIEW475E142D4E000

Name: Lay Summary

View: Justification, Objective, &amp; Research Design

## Justification, Objective, & Research Design

- 1 **\* Provide context, justification, and scientific/scholarly rationale for the study:**

Currently CT is used to diagnose patients with Traumatic brain injury. A significant portion of these patients will get an MRI for an accurate assessment of the extent of the injury. In recent years, there has been a significant advancement in MRI techniques that have the potential to diagnose TBI even more accurately and may have enough sensitivity for being a prognostic marker. In this study we wish to systematically study the imaging markers obtained from diffusion tensor imaging, susceptibility-weighted imaging, MR spectroscopy, resting state MRI, and arterial spin labeling on TBI patients and assess them for their sensitivity at the acute stage and to determine which of the imaging markers have the highest sensitivity for longitudinal follow-up of patients.
- 2 **\* What is the purpose/objective of this study?**

The objective of this study is to identify advanced MR imaging markers that can serve as a prognostic marker in the evaluation and management of traumatic brain injury patients.
- 3 **\* Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:**

This study will recruit 40 patients each classified as mildly injured (GCS 13-15), moderately injured (GCS 9-12) and severely injured (GCS



3-8). Each of these subjects will obtain MRI at four different time points. The first MRI is obtained within the first ten days following injury. The second MRI is obtained about one month post-injury. The third MRI is obtained about 6 months post-injury. The fourth MRI is obtained about 18 months post-injury. During each of these time points, information from novel imaging techniques such as diffusion tensor imaging, MR spectroscopy, susceptibility-weighted imaging, arterial spin labeling and resting state MRI will be obtained. We will also concurrently obtain information from a battery of neuropsychological tests to correlate with the MRI findings whenever possible. Imaging information and cognitive test scores will also be obtained from age-matched normal volunteers at two different time points separated by 6 months. This data will be useful for comparison with each of the patient cohorts and will also provide normal variability and normative trend information for comparisons.

ID: VIEW43B257658E400  
Name: Justification, Objective, &  
Research Design

[View: Summary & Supporting Literature](#)

## Summary & Supporting Literature

### 1 \* Provide a summary of current literature:

Computed Tomography is the first line imaging tool for assessing TBI as it is convenient, quick, and provides a good measure of clinical assessment which leads to appropriate therapeutic intervention such as removal of extra-axial hemorrhage. MRI is used when CT is unable to explain the clinical condition of the patient as it is more sensitive than CT in detecting traumatic lesions especially those from diffuse axonal injury during the acute and the subsequent recovery phase following the injury. It is believed that TBI results in a combination of cytotoxic injury and extracellular vasogenic edema in the early stages, which is followed by increased extracellular fluid. The brain cell death (cytotoxic injury) and expansion of the CSF spaces ultimately result in cerebral atrophy or encephalomalacia. Conventional MR is unable to demonstrate these important microscopic injury that occur in the white matter. Both conventional MR and CT are well known to underestimate the extent of DAI injury and have correlated poorly with the final outcome. Recent literature suggests that novel MR imaging techniques are much more sensitive in demonstrating changes that occur even with mild TBI compared to the conventional MRI techniques and have the potential to provide important prognostic data. These techniques include diffusion tensor imaging (DTI), MR spectroscopy (MRS), susceptibility-weighted imaging (SWI) and functional connectivity MRI (fcMRI).

The ability to study the change in random motion of proton in water in-vivo is the basis for DW-MRI. Preliminary reports indicate DW-MRI and DTI, are more sensitive than conventional MRI in detecting restricted proton motion resulting from cytotoxic edema in ischemic brain tissue.<sup>48,49,52</sup> Restricted proton motion results in a decrease in the apparent diffusion coefficient (ADC) of water and increased signal intensity on diffusion-weighted images. The changes in water mobility is best be visualized using DTI and fiber tracking and provides evidence of axonal damage. Magnetic resonance spectroscopy (MRS) offers a unique opportunity to non-invasively measure cellular biochemical's in vivo. In the brain metabolites such as the neuronal and axonal marker, N-acetylaspartate (NAA), creatine (Cr), the myelin breakdown products choline (Cho) and myo-inositol(ml), and lactate (Lac) which is a marker for anaerobic metabolism, can be measured to evaluate metabolic changes that occur with brain injury. Studies report a decrease in NAA and increased Cho/Cr ratio within injured regions of the brain that appear normal on conventional MRI. These biochemical changes as monitored by MRS potentially provide very early evidence of injury to brain cells prior to any structural changes that are visualized by conventional MRI.

In MRI, evaluation of hemorrhagic lesions involves the use of a gradient echo technique that is sensitized to the alteration in the magnetic field caused by deoxyhemoglobin associated with the hemorrhage. However, even this technique is unable to demonstrate significant amounts of micro-hemorrhage in the brain parenchyma resulting from TBI. Recent development of susceptibility-weighted imaging technique has shown to be a powerful tool that exaggerates the phase differences created by oxy- and deoxyhemoglobin due to their magnetic susceptibility differences and is able to clearly demonstrate micro-hemorrhages.

It is well known that TBI leads to slowed information processing in the brain suggesting that the resting state network may be impaired in patients with TBI. Resting state functional MRI (also called functional connectivity MRI, fcMRI) studies have demonstrated synchronous fluctuations in functionally related regions of the brain. In the absence of external stimuli, concurrent patterns of BOLD activation have been



shown within specific systems (e.g., the motor cortex) with dynamic data acquired while the participant is at rest (resting-state). These concurrent signals depict a degree of connectivity between concurrent but spatially disparate functional regions and as such, these studies are typically called functional connectivity experiments. Together diffusion tensor imaging and functional connectivity information can provide valuable objective data that may help to explain and correlate with the cognitive impairment that could be evaluated using neurocognitive tests in patients with TBI.

To date there have been no studies that have examined the combined use of these various new powerful techniques in patients with TBI. Overall, parameters derived from these novel techniques provide an insight into the biophysical, biochemical and vascular changes in various regions of the brain. Further information from each of these individual techniques is complementary and therefore the combined information will provide an accurate assessment of the extent of brain injury and provide important objective prognostic imaging marker that will help to predict outcome on admission.

2 **If available, upload your supporting literature here:** [\(Uploading Help\)](#)

CT and MRI	1/21/2009 6:00 PM	1/21/2009 6:00 PM
DTI_and_outcome	1/21/2009 6:26 PM	1/21/2009 6:26 PM
Functional Connectivity	1/21/2009 5:58 PM	1/21/2009 5:58 PM
spectroscopy1	1/21/2009 6:22 PM	1/21/2009 6:22 PM
Spectroscopy2	1/21/2009 6:22 PM	1/21/2009 6:22 PM
susceptibility-weighted_imaging	1/21/2009 6:27 PM	1/21/2009 6:27 PM

3 **\* Provide a list of 3 keywords or search terms (1 per line) relevant to your research that would help potential participants find your study using search engines:**

\* Keyword 1: diffusion tensor imaging

\* Keyword 2: magnetic resonance spectroscopy

\* Keyword 3: traumatic brain injury

ID: VIEW4427429624400  
Name: Summary & Supporting Literature

[View: Study Design](#)

## Study Design

1 **\* What is your study design?**

- ☐ Drug, Approved
- ☐ Group Discussion
- ☒ Neuropsychological or psychophysiological testing

- ☐ Drug, Phase III
- ☐ Chart/record Review, Retrospective
- ☒ Other
- ☐ Device
- ☐ Pilot
- ☐ Survey/questionnaire
- ☐ Audio or video recording/photographing
- ☐ Intervention-Psychosocial or Behavioral
- ☐ Laboratory/specimen collection
- ☐ Use of existing banked specimens
- ☐ Chart/record Review, Prospective
- ☐ Interview
- ☐ Drug, Phase IV
- ☐ Deception
- ☐ Drug, Phase I
- ☐ Other Psychosocial or behavioral procedures
- ☐ Drug, Phase I/II
- ☐ Specimen banking
- ☐ Drug, Phase II

ID: VIEW45627CDF92400  
Name: Study Design

View: Study Design - Other

## Study Design - Other

- 1.1 \* You stated your Study Design was Other, specify:  
Magnetic Resonance Imaging

ID: VIEW4574AD3E24400  
Name: Study Design - Other

View: Study Procedures

## Study Procedures

### 1 \* Describe all research procedures:

This research study will recruit a total of 120 patients with traumatic brain injury admitted to the Shock Trauma Center (STC). MRI of the brain will be performed within 10 days following injury, at about 1 month, 6 months, and 18 months post-injury. Based on the severity of head injury, the patients will form three sub-groups of mild (GCS 13-14), moderate (GCS 9-12), and severe injury (GCS 3-9) respectively, with 40 patients in each sub-group. Patients may be recruited into the study provided they have a clinical presentation consistent with head trauma. Imaging and cognitive testing results from each of the sub-groups will be compared with the normal control population (n=30). Care will be taken to match the average age of the normal controls as best as possible with the three patient groups. The patients and controls will undergo a battery of neurocognitive tests concurrent with the imaging session.

**Neurocognitive Tests:** In conjunction with the MRI visit, standard clinical assessment information will be captured at the STC and the University of Maryland Head Injury Rehabilitation Center. The Glasgow Coma Scale (GCS) and the levels of cognitive functioning based on the Rancho Los Amigos scale or typically called the Rancho Level of Cognitive Functioning will be administered. The Rancho scale rates the patients from 1-8 with one representing a no response state to a score of 8 representing a purposeful, appropriate state. The Military Acute Concussion Evaluation (MACE) will assess orientation, immediate memory, concentration and delayed recall.

A battery of assessments will be captured concurrent with each of the imaging time points, with assessments chosen to match the patient's current rehabilitation status. During discharge from the primary hospital (Shock-trauma center) and during each of the three sub-sequent visits, the subjects will be assessed on the Disability Rating Scale (DRS), Rancho Los Amigos Scale, Orientation Log (OLOG) and the Satisfaction with Life Scale (SWLS). The Functional Independence Measure (FIM) will be performed in outpatient traumatic brain injury rehabilitation. The advantage of the DRS is in its ability to track an individual from coma to community. Measurements in this scale span a wide variety of items including impairment, disability and handicap. The maximum score a patient can obtain on the DRS is 29 representing extreme vegetative state to a zero representing no disability. The FIM is the most widely accepted functional assessment measure in use in the rehabilitation community. It is an 18-item ordinal scale related to functioning day to day from locomotion to toilet transfer and is used with all diagnosis within a rehabilitation population. It is considered the most useful measure for assessment of progress during inpatient rehabilitation. Each of the 18 items is rated by a qualified rater with scores going from 1 for complete dependence to 7 for complete independence. Typically the patient is scored at admission and discharge. The OLOG was developed to measure orientation to time, place, and circumstance in a rehabilitation population. The OLOG can be used for serial assessment of orientation to document changes over time. In our case we will be administering OLOG to assess post traumatic amnesia during each of the imaging time points. The SWLS is a measure of life satisfaction of an individual with a brain injury. It consists of 5 statements and the patients responses are scored from 1-7 (strongly disagree to strongly agree). The sum of the scores then provides a measure for life satisfaction. Finally, all subjects will be administered the Glasgow Outcome Scale – Extended (GOSE) at discharge and at each of the imaging time points. It measures eight categories from Dead to upper good recovery. Prior to the administration of cognitive testing, a cognitive screening measure (MMSE) will be used to determine eligibility for cognitive testing participation. All eligible participants will also take part in the Automated Neuropsychological Assessment Metrics (ANAM) which is administered on the computer and assesses speed and accuracy of attention, memory, and thinking ability. All the neuropsychological assessments will be performed by trained individuals.

#### Imaging Tests:

MRI of the brain will be obtained at four time points for the patients included in study as stated above. Two MRI examinations of the brain will be performed separated by about 6 months on the control subjects. Images and cognitive test scores from the control subjects will provide information on normative values and their test-retest reliability which can be used for an objective statistical comparison and interpretation of the data from the TBI patients.

**MRI protocol:** All MR examinations will obtain conventional MRI that is routinely performed on the TBI patients. This includes conventional T1 and T2-weighted images, Fluid-attenuated inversion recovery (FLAIR), gradient echo images and susceptibility-weighted images. In addition, images from the following techniques will also be obtained : diffusion tensor imaging, three-dimensional MR spectroscopy, and functional

connectivity scans. The total scan time during each visit will be about 75-80 minutes.

The diffusion tensor images will provide information on the integrity of white matter tracts. MR spectroscopy will provide information on biochemical changes following injury. Susceptibility-weighted images will provide information on the hemorrhagic burden following injury and functional connectivity will provide information on changes to resting state networks. Together these techniques provide the biophysical, biochemical, vascular and functional status of the TBI patients. The comprehensive information from these techniques will be used to monitor the time course of changes in these parameters to determine the most sensitive and specific imaging parameters that can accurately predict the outcome on TBI patients.

2 \* Describe all procedures already being performed for diagnostic or treatment purposes:

Conventional MRI of the brain is often a standard procedure during the initial days following injury. This includes the standard T1 and T2-weighted imaging, FLAIR, gradient echo imaging, susceptibility-weighted imaging, diffusion-weighted imaging and diffusion tensor imaging. Other techniques described above including MRS, SWI and functional connectivity MRI are not necessarily standard of care at our institution.

Conventional MRI is not necessarily ordered during follow-up of patients that have suffered TBI. Individuals who receive MRI that is not part of standard care will be cleared for participation by the clinical trauma staff, making sure they are medically stable enough to undergo MRI.

3 \* Describe participants' duration of participation:

We expect the participants to be enrolled in this study for about 18 months and not exceeding 20 months. The actual time spent on this study will not be more than 8-10 hours total during these 18 months. Transportation time will depend on the distance the participation needs to travel to the MRI center and this is in addition to the 8-10 hours.

4 \* Describe the duration of the entire study:

The duration of the study is for three years. We expect to complete recruitment in the first year. Complete all the data collection by 24-30 months and the final six months will be for data analysis.

5 \* Describe any additional participant requirements:

Patients who receive MRI that is not part of standard care must be medically stable enough to transport prior to arrangement of MRI. The clinical trauma staff will ensure that patients who undergo research MRI are medically stable enough to do so.

There are no additional participant requirements other than the fact they should satisfy the safety requirements for MRI scanning. Because there is transportation involved we will restrict the study to patients residing within 90 minutes of driving time and are able and willing to travel for followup visits to and from the MRI center.

ID: VIEW4540FA8938400  
Name: Study Procedures

View: Research Related Risks

## Research Related Risks

1 \* Individually list each research-related risk, using a separate line for each. Next to each risk, delineate the likelihood/seriousness of the risk, and the provisions for minimizing the risk:

This research protocol has no risks associated with it above and beyond that normally associated with MR imaging. All patients and normal control subjects will have to pass the MRI Checklist to be eligible for the study, and MRI eligibility will be checked before each MRI

appointment. Patients who are undergoing MRI that is not ordered as part of standard care will be evaluated and cleared for medical stability for MRI by clinical trauma staff prior to MRI. They must be able to be transported without a monitor or nurse.

**Metal Implants:** Some metallic implants are contraindicated for MRI. Routine established screening for such implants is performed before every patient is taken into the MRI scanner. Similar precautions will be used while enrolling patients for this study.

**Aneurysm clips/intracranial clips:** It is possible that some patients may not be eligible for MRI because they have had an aneurysm clip or intracranial clips and will also depend on the make and how long ago such a procedure was performed. Once again the established screening process for all patients obtaining an MRI will screen such patients out and if they are contraindicated will not be enrolled for this study.

**Cardiac Pacemakers:** It is known that malfunction of cardiac pacemakers may occur within the magnetic field environment. No patients or control subjects will be recruited that have a pacemaker.

**Implantable programmable device, implanted defibrillator/pump, neuro/bio-stimulator:** High magnetic fields can affect any of these devices. Therefore no patients or control subjects will be recruited that have any of these devices.

**Claustrophobia:** 2-3% of the patient population experience claustrophobia in the MRI environment. Many of these patients exhibit these symptoms for the first time. If any patient or control subjects discover that they are claustrophobic we will remove them from the scanner and such patients will not continue on with the rest of the study. We will ensure that everyone recruited into this study will be as comfortable as possible in the MRI environment. The scanners have intercom systems and video cameras that allow the operator to remain in constant visual and auditory contact with the subjects at all time. Further we will provide the option of watching a video or listening to their favorite music while they are being scanned. They will also be provided with an "attention" button that they can press to get the immediate attention of the MRI operator.

It is necessary that the subject remain completely still during image acquisition and relatively still throughout the duration of his stay in the magnet. This can sometimes result in temporary muscle stiffness and/or soreness. If the subject should become uncomfortable he can use the intercom system at any time to request to be removed.

#### Patient Identification & Breach of Confidentiality

All data will be obtained using a code identifier. The coded data will be available only to the PI and his research group. This will minimize the risk of breach of confidentiality.

#### Incidental findings:

Incidental findings on clinical patients are always reported. If during the imaging the operator, the PI or any of the co-PI note any feature in any image that is remotely questionable on patients or normal control subjects, a review of the images will be requested from a radiologist. If the radiologist determines that an abnormality is present unrelated to the study, contact will be made with the subject and counseling will be provided to obtain appropriate medical attention.

#### Neurocognitive Testing:

The cognitive assessments are designed to test your attention, memory, and mental processing speed. You may find some of these tasks more difficult or frustrating and may cause fatigue. The duration of the assessments has been optimized to minimize fatigue. However, you can request a break from the test, or choose to withdraw from the tests at any time if frustration or fatigue becomes significant.

ID: VIEW43B3485673400  
Name: Research Related Risks

View: Potential Benefits

## Potential Benefits

1 \* Describe the potential benefit(s) to participants:

This study does not address the treatment of patients and hence there is no change in the course of their normal clinical care. However individual subject may benefit from this research due to the increased level of observation and the availability of imaging and cognitive testing that will be done as a result of the research.

2 \* Describe the importance of the knowledge expected to result from the study:

There has been proliferation of advanced MR imaging techniques that shown some benefits in characterizing brain injury over and beyond what the current imaging techniques are able to do. Further the conventional imaging techniques are often non-conclusive or do not completely explain the clinical condition of the patient. The new advanced imaging techniques however have not been evaluated systematically on traumatic brain injury patients with varying injury severity. This study will systematically study these techniques in the context of TBI and follow the sequelae of the injury to arrive at the best prognostic and objective imaging markers. An immediate benefit resulting from this study is a better understanding of the long-term brain-behavior connection among the injured patients including those returning from wars. Further, an objective imaging marker will be very beneficial in the development of therapeutic regimens whether they are pharmacological or rehabilitative therapies.

3 \* Describe how the potential risks to participants are reasonable in relationship to the potential benefits:

Although this study may not benefit the current participants, the benefits to the society are very large and translate to benefits to our veterans. Very little is known regarding the sequelae of TBI. Participating in this research which has minimal risks is going to advance our knowledge of TBI and allow us to objectively predict the outcome of patients with some confidence. Furthermore, risk involved from the MR imaging is minimal, and all data will be obtained under a code identifier. It is possible that a new disease process could be discovered in the control subject population after completion of an elective MRI.

ID: VIEW43B34A7DE3400  
Name: Potential Benefits

[View: Privacy](#)

## Privacy

1 \* Describe how you will ensure the privacy of potential participants:

All consent and study procedures will be conducted in a private setting. The patient has the right to refuse access of the study staff and withdraw at any time.

2 \* Describe the location where potential participants will receive research information:

Patients that are admitted to the shock trauma center of the University of Maryland Medical Center will be made aware of the research information, and given a packet detailing research procedures. After the patient is stabilized following initial trauma, the research nurse will make the patients (if they are conscious), the legally authorized representative (LAR) aware of the study and will offer the opportunity to read the consent form.

3 \* Describe potential environmental stressors that may be associated with the research:

The main stressor for this study is the MRI environment and in particular during the first time point of imaging immediately after injury. However for most injured patients MRI may be required clinically. Other stressors include continued participation in the study especially among the mildly injured subjects.

4 \* Describe how privacy will be protected through each phase of the study and detail the specific actions the study team will take to ensure adequate privacy areas:

Once identified as a potential study subject, the patient/patient's legally authorized representative will be approached by trained research staff in the patient's room or in a family conference room on the unit to ensure privacy. If the patient/patient's legally authorized representative is agreeable to hearing more about the research study, the study and consent procedures will be explained in privacy. All research data that is collected including imaging and data collection forms will be coded and will not contain the patient's medical record number, name or any other identifying information. Only the PI and his immediate research staff having access to the identifiers. Every effort will be made to conduct research interactions in a private matter including consenting for the study. The research staff has been trained in confidentiality practices and are sensitive to the need to keep patient interactions private.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Arm Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of information.

ID: VIEW43B24BD857800  
Name: Privacy

View: Confidentiality

## Confidentiality

1 \* Will research data be linked to individual participants (identifiable)?

☒ Yes ☐ No

2 \* Will research data be de-identified (no links or codes maintained)?

☐ Yes ☒ No

3 \* Where will research data be kept?

Research data that is captured on media from the scanners will be kept in a secured locked location within the PI's office. Data that has been transferred to workstations will be password protected computers or in a locked research office accessible only to trained research personnel.

4 \* How will such data be secured?

All research data including the imaging and cognitive data will be coded. An alpha-numeric code will be assigned to data obtained from patients and control subjects. DICOM headers from the imaging data will be stripped of identifying information before images are stored in the secure database.

5 \* Who will have access to research data?

Only the PI and his research staff will have access to the research data.

6 \* Will study data or test results be recorded in the participant's medical records?

☐ Yes ☒ No

7.1 \* Will results of specific tests be revealed to the research participant or his/her doctor?

☐ Yes ☒ No

7.2 \* Will results of the overall study be revealed to the research participant or his/her doctor?

☐ Yes ☒ No

7.3 \* Explain why or why not:

This is a research study that attempts to understand the value of novel imaging techniques in accurately and objectively diagnosing TBI. The results of cognitive tests will be provided to the subjects upon request. However no interpretation will be provided. Similarly upon request some sample images will be provided but with no interpretation. The results of the overall study will be made public through publications and the participants and physicians will have access to such information.

8 \* Do you plan to obtain a Certificate of Confidentiality?

☐ Yes ☒ No

9 \* Discuss any other potential confidentiality issues related to this study:

There are no other potential confidentiality issues resulting from this study.

ID: VIEW43B49CBDC800  
Name: Confidentiality

View: HIPAA Waivers

## HIPAA

1 \* Select one:

- ☐ This research will require a HIPAA privacy waiver (for entire study)
- ☒ This research will require a partial HIPAA privacy waiver (for recruitment)
- ☐ Neither of the above

2 If your study requires a HIPAA Authorization Form, upload that document here: (Uploading Help)

There are no items to display

ID: VIEW453FC2F168C00  
Name: HIPAA Waivers

View: HIPAA - Partial Privacy Waiver

## HIPAA - Partial Privacy

1 \* Provide a brief description of the Protected Health Information (PHI) for which use or access is necessary (including sources of the PHI):



age  
 prior clinical history  
 initial diagnosis after TBI  
 Glasgow coma scale  
 mechanism of injury  
 use of drug or alcohol  
 CT scan report  
 Glasgow outcome scale  
 functional independent measure

**2 \* Provide a plan to protect the identifiers from improper use and disclosure and to destroy the identifiers at the earliest opportunity consistent with the conduct of the research (or provide a health or research justification for retaining the identifiers):**

All hard-copy data will be stored in a designated locked office and stored in secured, locked storage cabinets. Electronic data, including images will be stored in a password protected computer. Only designated members of the research team will have access to the study office and data storage equipment. Data that is obtained for clinical purposes in conjunction with this study will be duplicated, and coded. The DICOM header of the images which may have patient identifiers will be stripped of identifying information before the data is stored on the secured servers.

Records will be maintained within the guideline of the federal regulations, specifically two years after the termination of the study. At study completion all records will be maintained in a locked storage area. All electronic records will be copied to a DVD or other storage media and maintained in a locked storage area by the principal investigator. At the expiration of the required time of retention of study records, hard-copy data will be shredded and electronic copies will be destroyed.

**3 \* Describe how initial contact will be made and briefly sketch introductory remarks:**

Initial contact will be made with subjects after it has been determined they meet the inclusion criteria. If patient meets the inclusion criteria the study staff introduces themselves as employees of the University of Maryland to the patient or to the legally authorized representative. The study staff will then explain the study during the informed consent discussion

ID: VIEW43D663426A800  
 Name: HIPAA - Partial Privacy Waiver

View: Recruitment

## Recruitment

**1 \* Describe plans for recruitment, including the identification of potential participants and initial interactions with them:**

Initially, only the medical record will be reviewed to determine if the patient meets the inclusion/exclusion criteria. Trained research staff will approach the nursing staff to request permission to approach eligible patients. The patient or the patient's legally authorized representative would then be approached to provide consent for the research procedure. The following would be said: "Hello, I am (STAFF'S NAME) and I am on the research team of Dr. Gullapalli and Dr. Aarabi. Because you have (or your next of kin has) suffered a head injury, I would like to talk to about the option to participate in a research study pertaining to head injury."

The study would be explained in full, including the right to refuse without penalty, the right to refuse access to research staff, and the right to

discontinue any research procedure at any time. The participants will be given a chance to ask any questions or address any concerns about the study. Copies of the consent form will be provided for them to read.

Letters explaining the study may be left with eligible participants and their families. These letters contain information about aspects of the study: what's involved in participation, potential risks, ability to withdraw consent at any time without penalty, and so fourth. We intend for this information to lessen any pressure the individual may feel to immediately decide on participation. These individuals will also be provided with a copy of the consent form to review.

The control group will be recruited through advertisement in the University's "Voice" and other advertising channels including the posting of fliers around the campus.

2 **\* Describe measures that will be implemented to avoid participant coercion or undue influence:**

In the process of recruitment it will be made very clear that there is absolutely no requirement for the patients to agree to participate in the research and no stigma whatsoever will result should they decide not to participate. It will also be made clear to the patients that the scanning will not directly help them but has a strong potential of helping us understand TBI may help future victims of TBI. There will be no coercion during the recruitment of the control group including those personnel that may belong to the PI's laboratory or the co-investigator's meeting.

3 **\* Who will recruit participants for this study?**

- ☒ PI & Staff  
☐ PI  
☐ Third Party

ID: VIEW449A0764FBC00  
Name: Recruitment

[View: Advertising](#)

## Advertising

1 **\* Will you be using advertisements to recruit potential participants?**

- ☒ Yes ☐ No

ID: VIEW4517F2C65B000  
Name: Advertising

[View: Advertising Detail](#)

## Advertising Detail

1.1 **Select the mode(s) of advertising:**

- ☐ Radio  
☐ Internet

- ☒ Print
- ☐ Television
- ☒ Other

**1.1.1** [If Other, specify:](#)  
Flier

**1.2** [Provide exact language of all proposed advertisement\(s\):](#)  
Paid Volunteers Needed

Men and Women above the age of 18 years are needed to participate in a Magnetic Resonance Imaging Study to develop Prognostic MR Imaging Markers of Traumatic Brain Injury. Compensation will be provided for your participation.

For more information:

Call: 410-328-6443  
410-328-2099  
Email: ktaylor@umm.edu  
OR  
visit  
Magnetic Resonance Research Center  
110 S. Paca St, MRI Suite #104  
Baltimore, MD 21201

**1.3** [Upload advertisement\(s\) here:](#) [\(Uploading Help\)](#)

Name	Created	Modified Date
<a href="#">Volunteer Recruitment Flier</a>	4/21/2010 6:04 PM	4/21/2010 6:04 PM

ID: VIEW4574C9481E800  
Name: Advertising Detail

View: Research Related Costs

## Research-Related Costs

- 1** [\\* Is the study's financial supporter \(e.g. commercial sponsor, federal or state grant or contract, private foundation, physician-sponsor\) covering any research-related costs?](#)  
Yes

**1.1** [If Yes, check all that apply:](#)

- ☐ Investigational Procedure(s)
- ☒ Research-Related Services (tests, supplies, exams, x-rays, or consultations required in the study)

☐ Investigational or Study Device

☐ Investigational or Study Drug

**1.2** If No, who is responsible for payment?

**2** \* Who is responsible for the uncovered research-related costs?

☐ Participant

☐ Sponsor

☐ Other

☐ UMB

☒ There will be no uncovered research-related costs

**2.1** If Other, specify:

**3** If the participant is responsible for any research-related costs, identify and estimate the dollar amount:

The participant is not responsible for any research related costs.

ID: VIEW43CA73E7CC800  
Name: Research Related Costs

View: Participant Selection

## Participant Selection

**1** \* How many local potential participants (or specimens, or charts) do you anticipate will be screened for this study?

170

**2** How many participants (or specimens, or charts) will be enrolled/used for this study?

\* Local - the number being enrolled at this site or will be consented using a UMB-approved Informed Consent Document:

150

\* Worldwide - the number that will be enrolled total at all sites:

150

**3 Gender:**

- ☒ Male
- ☒ Female

**4 Age(s)**

- ☐ Nonviable Neonates or Neonates of Uncertain Viability
- ☐ 0 to 27 days (Term newborn infants)
- ☐ 28 days to 12 months (Infant)
- ☐ 13 months to 23 months (Toddler)
- ☐ 2 to 5 years (Preschool)
- ☐ 6 to 11 years (Child)
- ☐ 12 to 17 (Adolescents)
- ☒ 18 to 44 years (Adult)
- ☒ 45 to 64 years (Middle Age)
- ☒ 65 plus years (Elderly)

**5 Race/Ethnicity:**

- ☒ All Races Included
- ☐ American Indian or Alaskan Native
- ☐ Asian / Other Asian
- ☐ Asian / Vietnamese
- ☐ Black or African American
- ☐ Hispanic or Latino
- ☐ Mixed Race or Ethnicity
- ☐ Native Hawaiian or Pacific Islander
- ☐ White

**6 Language(s):**

- ☒ English
- ☐ Chinese

- ☐ French
- ☐ Italian
- ☐ Japanese
- ☐ Korean
- ☐ Local Dialect
- ☐ Spanish
- ☐ Vietnamese
- ☐ Other

#### 6.1 Specify Other:

#### 7 \* Are you excluding a specific population, sub-group, or class?

☒ Yes ☐ No

ID: VIEW43B36EB5E8400  
Name: Participant Selection

View: Participant Selection Justification

## Participant Selection Justification

#### 7.1 \* Indicate your justification for excluding a specific population, sub-group, class, etc.:

Pregnant women are excluded from the study, as the effects of Magnetic Resonance Imaging on unborn fetuses are not well established. Pregnancy status in patients is determined by a pregnancy test on admission to Shock Trauma. Volunteers are made aware of the risks to unborn fetuses, and made aware that they should not participate if they believe they are pregnant or could become pregnant.

ID: VIEW4574CE0D6EC00  
Name: Participant Selection Justification

View: Vulnerable Populations

## Vulnerable Populations

#### \* Will you be recruiting ANY of the following Vulnerable Populations? (Select all that apply)

- 1
- ☒ Employees or Lab Personnel
  - ☐ Children
  - ☒ Women of Child-bearing Potential

- ☐ Educationally Disadvantaged
- ☒ Critically ill or Injured Patients
- ☒ Cognitively Impaired/ Impaired Decision Making Capacity
- ☐ Pregnant Women
- ☐ Wards of the State
- ☐ Terminally ill Patients
- ☒ Students
- ☐ Prisoners
- ☐ Emancipated Minors
- ☐ Fetuses
- ☐ Neonates
- ☐ Homeless or Economically Disadvantaged
- ☒ Emergency Room Patients
- ☐ Mentally ill
- ☐ Post Traumatic Stress Disorder (PTSD) Participants
- ☐ None of these applies.

ID: VIEW45627D2912400  
Name: Vulnerable Populations

View: Vulnerable Populations - Cognitively Impaired

## Vulnerable Populations - Cognitively Impaired

### 1 You chose "Cognitively Impaired" as a Vulnerable Population that you will be recruiting.

**\* Describe how will you obtain informed consent, protect subject confidentiality, and prevent undue coercion.**

The nature of this study dictates that we recruit patients who have suffered TBI. Because of the nature of the injury most of these patients may be impaired cognitively during the initial consenting process. Many of these patients will be represented by a legally authorized representative who will provide the consent. If after obtaining consent from this representative, the patient returns to his/her normal levels of cognition and then decides to withdraw from the study he/she will be removed from the study immediately.

A significant portion of the recruited population, particularly those among the mild and moderately injured groups, may have the cognitive capacity to consent. On such patients, we will obtain consent directly from the patient. All patients who are able to express willingness to participate in this study will be administered a standard Mini Mental Status Examination to determine the competency of the subject to sign the consent form (Please see the attached MMSE questionnaire). If the subject scores 22 or higher he/she will be considered competent to

consent for the study.

All patient information will be kept confidential. In the process of recruitment and it will be made very clear that there is absolutely no requirement for them to agree to participate in the study and no stigma whatsoever will result should they decide not to participate.

We will enroll patients in the proposed study based on evidence of TBI only. Ethnicity or gender is not an indication for either inclusion or exclusion of any patient.

ID: VIEW469631B294C00  
Name: Vulnerable Populations -  
Cognitively Impaired

View: Vulnerable Populations - Critically Ill or Injured Patients

## Vulnerable Populations - Critically Ill or Injured Patients

### 1 You chose "Critically Ill or Injured Patients" as a Vulnerable Population that you will be recruiting.

\* Describe how will you obtain informed consent, protect subject confidentiality, and prevent undue coercion.

The nature of this study dictates that we recruit patients who have suffered TBI. Because of the nature of the injury most of these patients may be critically ill or injured during the initial consenting process. Many of these patients will be represented by a legally authorized representative who will provide the consent. If after obtaining consent from this representative, the patient returns to his/her normal levels of cognition and then decides to withdraw from the study he/she will be removed from the study immediately. If at any time during the study the patients recover from their critical status, assessments regarding their competency to consent for the study will be made. They will be administered a standard Mini Mental Status Examination to determine the competency of the subject to sign the consent form (Please see the attached MMSE questionnaire). If the subject scores 22 or higher he/she will be considered competent to consent for the study.

All patient information will be kept confidential. In the process of recruitment it will be made very clear to the legally authorized representative that there is absolutely no requirement for them to agree to participate in the study and no stigma whatsoever will result should they decide not to participate. Similarly if any time during the course of the study, the patient is able to provide consent they will be provided similar information.

We will enroll patients in the proposed study based on evidence of TBI only. Ethnicity or gender is not an indication for either inclusion or exclusion of any patient.

ID: VIEW4696328F63C00  
Name: Vulnerable Populations -  
Critically Ill or Injured Patients

View: Vulnerable Populations - Emergency Room Patients

## Vulnerable Populations - Emergency Room Patients

### 1 You chose "Emergency Room Patients" as a Vulnerable Population that you will be recruiting.

\* Describe how will you obtain informed consent, protect subject confidentiality, and prevent undue



**coercion.**

The nature of this study dictates that we recruit patients who have suffered TBI. Because of the nature of the injury most of these patients may be critically ill or injured during the initial consenting process. Many of these patients will be represented by a legally authorized representative who will provide the consent. If after obtaining consent from this representative, the patient returns to his/her normal levels of cognition and then decides to withdraw from the study he/she will be removed from the study immediately. If at any time during the study the patients recover from their critical situation, assessments regarding their competency to consent for the study will be made. They will be administered a standard Mini Mental Status Examination to determine the competency of the subject to sign the consent form (Please see the attached MMSE questionnaire). If the subject scores 22 or higher he/she will be considered competent to consent for the study.

All patient information will be kept confidential. In the process of recruitment it will be made very clear to the legally authorized representative that there is absolutely no requirement for them to agree to participate in the study and no stigma whatsoever will result should they decide not to participate. Similarly if any time during the course of the study, the patient is able to provide consent he/she will be provided similar information.

We will enroll patients in the proposed study based on evidence of TBI only. Ethnicity or gender is not an indication for either inclusion or exclusion of any patient.

ID: VIEW4696345E79C00  
Name: Vulnerable Populations -  
Emergency Room Patients

View: Vulnerable Populations - Employees or Lab Personnel

## Vulnerable Populations - Employees or Lab Personnel

1 **You chose "Employees or Lab Personnel" as a Vulnerable Population that you will be recruiting.**

**\* Describe how will you obtain informed consent, protect subject confidentiality, and prevent undue coercion.**

Volunteers will be recruited as part of the control group in this study. Employees or Lab Personnel over the age of 18 could be part of this control group. MRI procedures are noninvasive, there is no need to exclude vulnerable patient populations such as Employees or Lab Personnel. A standard Mini Mental Status Examination will be administered to determine the competency of the such employees & lab personnel to sign the consent form (Please see the attached MMSE questionnaire). If the subject scores 22 or higher he/she will be considered competent to consent for the study. All employees and lab personnel information will be kept confidential. In the process of recruitment it will be made very clear that there is absolutely no requirement for them to agree to be scanned and no stigma whatsoever will result should they decide not to participate. This groups' employment status cannot be impacted regardless of participation or not.

Ethnicity or gender will not be an indication for either inclusion or exclusion of any employee or lab personnel.

ID: VIEW469633E9E2800  
Name: Vulnerable Populations -  
Employees or Lab Personnel

View: Vulnerable Populations - Students

## Vulnerable Populations - Students

1 **You chose "Students" as a Vulnerable Population that you will be recruiting.**

\* Describe how will you obtain informed consent, protect subject confidentiality, and prevent undue coercion.

Volunteers will be recruited as part of the control group in this study. Students over the age of 18 could be part of this control group. MRI procedures are noninvasive, there is no need to exclude vulnerable patient populations such as students. A standard Mini Mental Status Examination will be administered to determine the competency of the students to sign the consent form (Please see the attached MMSE questionnaire). If the subject scores 22 or higher he/she will be considered competent to consent for the study. All student information will be kept confidential. In the process of recruitment it will be made very clear that there is absolutely no requirement for them to agree to be scanned and no stigma whatsoever will result should they decide not to participate. The academic standing of the students cannot be impacted regardless of participation or not.

Ethnicity or gender will not be an indication for either inclusion or exclusion of any student.

ID: VIEW46963920D2400  
Name: Vulnerable Populations -  
Students

View: Vulnerable Populations - Women of Child-bearing Potential

## Vulnerable Populations - Women of Child-bearing Potential

1 You chose "Women of Child-bearing Potential" as a Vulnerable Population that you will be recruiting.

\* Describe how will you obtain informed consent, protect subject confidentiality, and prevent undue coercion.

All women of child-bearing potential are made aware that the effects of Magnetic Resonance Imaging on unborn fetuses are unknown, and hence women are excluded from participation. Patients will be administered a pregnancy test to determine pregnancy status on admission to Shock Trauma. Volunteers will be not administered pregnancy tests, and so they are made aware that they should not participate if they believe they are pregnant or could become pregnant.

Pregnancy status is also asked at MR appointments in a private setting. The information is kept confidential along with all other study information.

ID: VIEW469639C6ED800  
Name: Vulnerable Populations - Women  
of Child-bearing Potential

View: Eligibility

## Eligibility

1 \* List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

Number Criteria	
[View] 1	Age 18 or older
[View] 2	Evidence of external head injury or facial trauma, or mechanism of injury consistent with brain trauma, including loss of consciousness or altered mental status.

## Number Criteria

[View] 3 Willingness to attend follow-up appointments, preferably with residence within 90 minutes driving time of University of Maryland Medical Center.

## 2 \* List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

## Number Criteria

[View] 1 Penetrating Head Injury

[View] 2 Status post trauma due to asphyxiation

[View] 3 History of white matter disease or neurodegenerative disorders including Multiple Sclerosis, Huntington's Disease, Alzheimer's Disease, or Pick's Disease.

[View] 4 History of treatment or diagnosis of psychiatric conditions: Major Depressive Disorder (MDD), Bipolar Disorder (BPD), Schizophrenia, or Dementia of any type.

[View] 5 History of Stroke or Myocardial Infarction

[View] 6 History of Brain Tumor

[View] 7 Preexisting contraindications for Magnetic Resonance Imaging (MRI)

[View] 8 Active Duty Military Status

[View] 9 Police custody or prisoner status

[View] 10 Pregnant women

**After entering the inclusion and exclusion criteria above, click the Save link. CICERO will automatically generate a printable Eligibility Checklist for you to use in your research. To review the checklist, click on the resulting link below. This checklist is also available under the Documents tab of this application.**

Eligibility Checklist for HP-00040713\_10 v11-14-2010-1289770799899(0.01)

If you created additional Eligibility checklists outside of CICERO, you may upload them here. If you need a template, you can download it by clicking [HERE](#). The checklists you upload will also be available under the Documents tab of this application.

Name	Created	Modified Date
Volunteer Eligibility Checklist	4/23/2010 1:12 PM	4/23/2010 1:12 PM

ID: VIEW43B34B79AC400  
Name: Eligibility

View: Sample Size / Data Analysis

## Sample Size / Data Analysis

### 1 \* Provide your rationale and sample size calculations for the proposed target population:

Retrospective analysis of diffusion-weighted imaging data on trauma patients showed that the peak and average apparent diffusion coefficient differs at least by about 15% between each of the three groups of patients. In the calculation of our sample size of 40 patients in

each group, we have assumed that the mean values of the each of the imaging metric will differ by at least 15% between each group and that the standard deviation of these measures will be about 15% of the mean. To detect a significant (at 5% level) difference of at least 15% in the means of any two groups at a power of at least 0.9, the number of subjects in each of the injury group that need to carry on till the end of the study is 28. However we will obtain data on 40 patients in each of the cohorts to allow for other unexpected variables.

Unexpected variable mainly includes attrition from patients not following through with their scheduled appointments. To reduce this attrition we have already restricted the patient population that enters this study, as we are only going to choose the patients that have opted to use the University of Maryland Head Injury Rehabilitation Center at Kernan Hospital and those that live within 90 minute driving distance of the Medical Center. We have assumed an attrition rate of 15% per time point for each cohort.

- 2 \* Provide your plan for data analysis. Include in your description the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how will the analyses proposed relate to the primary purposes of your study:

The primary purpose of the study is to find imaging markers that best describe the clinical condition of the patient. For this whole brain and regional analysis of the brain imaging data will be analyzed.

Whole brain analysis: Specific data will be extracted from each of the imaging techniques at the whole brain and regional levels. From diffusion tensor imaging, we will obtain whole brain apparent diffusion coefficient (ADC) values, and fractional anisotropy values. These will be further compartmentalized into whole brain white matter and gray matter. From susceptibility-weighted imaging we will extract the hemorrhagic burden value which is representative of the fraction of brain pixels exhibiting hemorrhage including those from microvessels. From the spectroscopy data we will deduce the whole brain N-acetylaspartate (NAA), choline (Cho), creatine (Cre) and lactate (Lac). Arterial spin labeling will provide information on whole brain, gray matter and white matter perfusion. For all the above techniques voxel based morphometry (VBM) analysis will also be performed. VBM allows voxel wise comparison of grouped imaging data after transforming individual brain images to a standardized atlas and presents maps of regions that are significantly different in the specific parametric response between any two groups. Analysis of variance will also be used and adjusted for age and gender.

Regional Analysis: For all the above techniques regional data will also be acquired. Regional areas include the genu and splenium of the corpus callosum, basal ganglia, internal and external capsule, thalamus, caudate, frontal lobe, temporal lobe, and pons. From the functional connectivity data we will obtain information on the strength of primary motor and sensorimotor networks.

Scores from the various neuropsychological testing will be correlated with the various imaging parameters both at the whole brain and the regional brain level. Once again analysis of variance will be performed to assess the sensitivity of each of the imaging parameters described above that best captures the clinical condition of the patient. Logistic regression will also be used to determine if any of the imaging parameters at the whole brain and regional levels scale with the clinical status of the patient both at the time of the injury and during the course of recovery from the injury. Neuropsychological testing results will be compared between patients and controls, allowing for the testing of presence or absence of practice effects, and to determine the normative performance profile for individuals.

ID: VIEW444108B904800  
Name: Sample Size / Data Analysis

View: Participant's Payment

## Participant's Payment

- 1 \* Will participants receive payment (money, gift certificates, coupons, etc.) for their participation in this research?

☒ Yes ☐ No

View: Payment to Participants

## Payment to Participants

### 1.1 The participants will be compensated for:

- ☐ Meals
- ☒ Travel
- ☐ Lodging
- ☒ Parking
- ☐ Other
- ☒ Time

#### 1.1.1 If Other, specify:

### 1.2 What is the total dollar value of the payments over the duration of the study?

398.00

### 1.3 Describe the timing and distrubution plan for the payment (schedule, means etc)?

The patient participants total compensation for participating in this study will be \$300.

Patients will be compensated for their travel to and from the MRI center. They can choose their own transportation or transportation will be provided by us. If patients are discharged and must travel for their initial MRI, they will be given \$20 compensation for transportation expenses. This compensation will be given to participants recruited before the modification who provided their own transport to their initial visit. We will provide \$20 for travel expenses per visit for the three follow-up visits following the initial admission to the hospital. Parking fees will be paid for separately by the study and will cost \$6 per visit.

Follow Up Visits: A payment of \$75 will be made at the first follow-up study visit (about one month), a second payment of \$75 will be made at the second follow-up study visit (about 6 months), and \$150 will be paid at the end of the 18 month visit.

Normal volunteers will be paid a lump sum compensation of \$100 for participation in the study. The compensation will be made available after their second visit. A partial compensation of \$25 will be made if the normal volunteers were only able to complete the first part of the study.

### 1.4 Method of Payment to be Used:

- ☐ Gift Certificate / Gift Card
- ☒ Check
- ☒ Cash

- ☐ Coupons
- ☐ Money Order
- ☒ Parking Voucher
- ☐ Other

#### 1.4.1 If Other, specify:

ID: VIEW4572330D9A800  
Name: Payment to Participants

View: Monitoring Plan Determination

## Monitoring Plan Determination

- 1 \* Will the investigator use/defer to the sponsor's Data Safety Monitoring Plan?
- ☒ Yes
  - ☐ No
  - ☐ N/A

ID: VIEW43C4161FB7C00  
Name: Monitoring Plan Determination

View: Monitoring Plan - Sponsor's Additional Information

## Sponsor's Monitoring Plan - Additional Information

- 1 List the membership of the Sponsor's DSM contact information. You may also attach a listing of members and the DSMP or the applicable Board contact information.

### Contact Name:

Dr. Richman, Charmaine C

### Contact Title:

Grants Manager, CDMRP

### Contact Affiliation:

Congressionally Directed Medical Research Program TBI, PTSD Programs

### Contact Role:

### Contact Documents:

There are no items to display

2 \* What are the criteria defined in the protocol to be used for decision making regarding continuation, modification, or termination of study?

Continuation of the study will be contingent on the continued funding from Congressionally Directed Medical Research Program. Since this is an imaging study, no modifications are expected. However, if modifications seem necessary because of hardware or software changes, approvals will be obtained from the HSRRB and the IRB at University of Maryland Baltimore. Since this study does not involve the administration of a drug and involves only imaging, it is highly unlikely that termination will occur due to any adverse events.

ID: VIEW457C620D95400  
Name: Monitoring Plan - Sponsor's  
Additional Information

View: Study Schedule

## Study Schedule

1 If you have a Study Schedule from the sponsor, upload the document below. You can also create the Study Schedule in Microsoft Excel or Microsoft Word, and upload the document (see HELP button on the right column for other formats): (Uploading Help)

Name	Created	Modified Date
Study Schedule	2/1/2009 11:04 PM	2/1/2009 11:04 PM

ID: VIEW43CA726D2F800  
Name: Study Schedule

View: Sample Collection

## Sample Collection

1 \* Will samples (blood, tissue, urine, etc.) be collected as part of this study?

☐ Yes ☒ No

ID: VIEW455990CB07800  
Name: Sample Collection

View: Behavioral Methods and Procedures

## Behavioral Methods and Procedures

You indicated on the "Type of Research" page that your study involves a behavioral method or procedure -

1 Select all behavioral methods and procedures which apply to this study:

- ☐ Key informant or semi-structured individual interviews
- ☐ Focus groups or semi-structured group discussions

- ☐ Audio or video recording / photographing
- ☐ Individual or group behavioral observations
- ☐ Psychosocial or behavioral interventions
- ☒ Surveys / questionnaires
- ☒ Neuropsychological or psychophysiological testing
- ☐ Deception
- ☐ Other psychosocial or behavioral procedures

ID: VIEW43CA77131A800  
Name: Behavioral Methods and  
Procedures

View: Surveys / questionnaires

## Surveys / questionnaires

- 1 List all questionnaires/surveys to be used in the study, including both standardized and non-standardized assessments:

Modified Rivermead Post-Concussion Symptom Questionnaire

Pre-Visit Questionnaire: measures change in occupational, residential, and health status between visits.

- 2 Upload a copy of all assessments/surveys: (Uploading Help)

Name	Created	Modified Date
Modified Rivermead	8/25/2009 2:00 PM	8/25/2009 2:00 PM
Pre-Visit Update Questionnaire	8/25/2009 2:01 PM	8/25/2009 2:01 PM

- 3 How much time are the surveys expected to require?

No more than 10 minutes.

- 4 Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (ie. Illegal activities)

☐ Yes ☒ No

- 5 Do any questions elicit information related to the potential for harm to self or others?

☐ Yes ☒ No

- 5.1 If Yes, what procedures are in place to assure safety?

ID: VIEW451BB93E1A800  
Name: Surveys / questionnaires



View: Neuropsychological or psychophysiological testing

## Neuropsychological or psychophysiological testing

- 1 List all of the tests to be used in the study, including both standardized and non-standardized assessments:

Glasgow Coma Scale (GCS)  
Mini Mental State Exam (MMSE)  
Rancho Los Amigos  
Disability Rating Scale (DRS),  
Functional Independence and Assessment Measure (FIMFAM),  
Orientation Log (OLOG)  
Satisfaction with Life Scale (SWLS)  
Military acute concussion evaluation (MACE)  
Automated Neuropsychological Assessment Metrics (ANAM)

- 2 Describe procedures related to all testing:

All tests will be conducted at the laboratory of the PI or at the Kernan Hospital rehabilitation center and will be overseen by Dr. Makley, Director of the Traumatic Brain Injury at Kernan. All the tests listed above are standard battery of tests performed on TBI patients and patients recovering from TBI. Trained personnel will be administering the tests at either of these places. All neuropsychological tests will be conducted just prior to the MRI examination in both patient and control samples. Patients will be evaluated with the MMSE prior to MRI to determine eligibility for participation in cognitive testing.

- 3 Upload relevant testing materials: [\(Uploading Help\)](#)

Name	Created	Modified Date
<a href="#">ANAM</a>	10/15/2009 10:42 AM	10/15/2009 10:42 AM
<a href="#">DRS</a>	4/7/2009 9:55 AM	4/7/2009 9:55 AM
<a href="#">FIMFAM</a>	4/7/2009 9:54 AM	4/7/2009 9:54 AM
<a href="#">GCS</a>	4/7/2009 9:54 AM	4/7/2009 9:54 AM
<a href="#">GOSE</a>	4/7/2009 9:57 AM	4/7/2009 9:57 AM
<a href="#">MACE</a>	5/27/2009 4:55 PM	5/27/2009 4:55 PM
<a href="#">MMSE</a>	10/15/2009 11:39 AM	10/15/2009 11:39 AM
<a href="#">orientation log</a>	4/7/2009 9:56 AM	4/7/2009 9:56 AM
<a href="#">Rancho</a>	4/7/2009 9:55 AM	4/7/2009 9:55 AM
<a href="#">SWLS</a>	4/7/2009 9:57 AM	4/7/2009 9:57 AM

- 4 How much time are the tests expected to require?

On most subjects the battery of tests can be completed in about an hour. It is unlikely that the test will take more than 2 hours on any patients.

- 5 Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (ie. Illegal activities)

☐ Yes ☒ No

6 Do any questions elicit information related to the potential for harm to self or others?

☐ Yes ☒ No

6.1 If Yes, what procedures are in place to assure safety?

All data will be kept confidential. Only a research ID number will be recorded in all paperwork.

ID: VIEW452C758B34000  
Name: Neuropsychological or  
psychophysiological testing

View: Informed Consent Process

## Informed Consent Process

1 \* Describe the Informed Consent process in detail:

After obtaining a partial HIPAA waiver to review medical records for recruitment into this clinical study, a clinical research staff member who is trained to obtain informed consent will review the medical record to determine if the patient is eligible to participate in this study. Once identified as a potential study participant, the patient or legally authorized representative will be approached for consent. It is anticipated that due to the nature and severity of the injuries, that a few patients may be able to provide consent.

For all subjects, staff members will consult with the primary care nurse to determine if the patient is able to speak with the recruiter, or the best time to approach the legally authorized representation. No family member will be approached before they have been advised by the clinical staff as to the status of their family member. The study procedures will be explained, and the legally authorized representative will be offered the opportunity to read the consent form and ask questions, including asking questions of the investigators if requested. The legally authorized representative, on behalf of the patient, will be asked if the patient would be interested in participating in this research study, and given time to consider the wishes of the patient prior to signing the consent form.

Legally authorized representatives will be told that their obligation was to try to determine what the prospective participant's would do if competent or if prospective participants wishes could not be determined what they thought was in the competent person's best interest. If willing, a signature will be obtained on the consent form, subjects will be given a copy of the signed consent form, and a copy will be kept on file in the research record.

The legally authorized representative identification form will be completed when consent is obtained per standard operating procedures, and a copy of this document will be maintained in the research records. If possible, an initial interview with the patient or an interview with the LAR will be conducted to obtain personal and demographic information.

If the patient's condition improves and he/she is able to provide consent, the study staff will describe the study to the patient. The patient will be allowed to ask questions, and given time to consider if he/she desires to continue in the study. If so, he/she will sign the same consent form. Given the injury severity associated with the study population, the evaluation to sign consent, the Mini-Mental State Exam (MMSE) will be administered to all study participants once they are able to provide their own consent. If the patient wishes to be withdrawn from the study, he/she will be immediately withdrawn.

Patients may also be recruited into the study if a clinically required MRI was obtained within ten days of injury. In such cases, because the clinically required MRI contains significant amount of information that is useful for research purposes, we will obtain consent from either the patient or the LAR for the followup part of the study, as well as the potential to obtain the remaining portion of the research MRI protocol

whenever possible as long as it is within ten days of injury.

Patients and their families may be feeling overwhelmed and may require time to think about participation. In these cases, the study team will provide them a letter explaining the study to eligible patients and their families (including their rights as a participant, an explanation of the study, and some frequently asked questions about MRI, and the contact information of the study staff) and a copy of the consent form to review. The patients or LAR may then contact the study team to ask questions or go through the consent process.

All normal subjects interested in participating in the study will be screened for eligibility for this study and MR compatibility. They will be explained the objective of the study, the cognitive testing components, and the MR imaging process before obtaining consent. They will be assured of complete confidentiality of the imaging and cognitive testing data.

2 \* Describe who will obtain Informed Consent:

The PI or a member of the PI's research staff will obtain the consent.

3 \* Describe the setting for consent:

Patients that are admitted to the shock trauma center of the University of Maryland Medical Center will be made aware of the research information. After the patient is stabilized following initial trauma, the research nurse will make the patients, or the legally authorized representative (LAR) if the patient is unable to consent, aware of the study, and will offer the opportunity to read the consent form.

Normal subjects will be consented in PI's laboratory or at the MRI center.

4 \* Describe the provisions for assessing participant understanding:

All patients who are able to express willingness to participate in this study will be administered a standard Mini Mental Status Examination to determine the competency of the subject to sign the consent form (Please see the attached MMSE questionnaire). If the subject scores 22 or higher he/she will be considered competent to consent for the study.

Since the Legally Authorized Representative (LAR) is the authority for medical procedures, they should be considered competent to render consent for a minimum risk study. The study team does reserve the right to administer the MMSE to the LAR at their discretion if they suspect that the LAR is unable to meet informed consent criteria (e.g. the LAR is unable to follow the explanation or consent dialog).

Normal subjects will also be administered the MMSE.

5 \* Describe the consideration for ongoing consent:

Ongoing consent may be necessary among patients who deteriorate over the course of the study. We will administer both the MMSE questionnaire and the consent form during each patient visit.

6 \* Describe the procedures for orderly termination of the study:

The patient may choose to terminate the study at any time. They will be immediately removed from the study upon request. The patient will be partially compensated based on the number of visits. The patient will be asked whether their previously obtained data may be used for research evaluation. If the patient wishes, all data from the patient will be destroyed and removed from our records.

The normal subject may choose to withdraw from the study at any time. Upon receiving this request from the subject, they will be asked whether the data obtained up to that point could be used for research evaluation. If the subject wishes, all data from the subject will be destroyed and removed from our records.

View: Consent Forms - Draft

## Consent Forms - Draft

- 1 Upload all of your Consent Forms for approval. Use only Microsoft Word. [\(Uploading Help\)](#)

Name	Created	Modified Date
Consent Form	12/22/2009 3:48 PM	4/21/2010 10:17 PM
Consent Form April 23 2010.doc	4/22/2010 3:55 PM	4/23/2010 12:55 PM
Consent form June 9 2010 (for Mod 9 - Most Recent)	6/9/2010 4:36 PM	8/9/2010 10:25 AM
Consent Form May 11 2010	5/12/2010 11:51 AM	5/12/2010 11:51 AM

**IMPORTANT NOTE:** the above list of consent forms (if any) are DRAFT versions. Under no circumstances should copies of these be distributed to patients/study subjects. If/when this research submission is approved by the IRB, this page will change and will show the Approved Consents. Approved consent forms will also be available for download and use from the "Documents" tab of the Submission's workspace (click Exit and then look for the Documents tab - approved submissions only)

### Instructions for preparing consent forms for approval by the University of Maryland, Baltimore IRB

According to UMB HRPP Policies and Procedures, readability of an informed consent document should be no greater than a 7<sup>th</sup> grade reading level. The IRB recommends the use of this website:  
<http://healthcare.partners.org/phsirb/consfrm.htm>

In order to measure readability using the Flesch-Kincaid reading level analysis function in Word, go to:

- TOOLS, then OPTIONS, then SPELLING AND GRAMMAR
- Select "Check grammar with spelling"
- Select "Show readability statistics"
- Click OK
- Proceed through the spell check, and when finished, the readability level should be displayed.

Formatting and fonts should be simple. Use 12 point Times New Roman font, bullets, and keep underlining, bolding, and italicized words to a minimum.

MOST CONSENT DOCUMENTS ARE COMPRISED OF SECTION HEADINGS WHICH ADDRESS THE FOLLOWING: Purpose, Procedures, Potential Risks/Discomforts, Potential Benefits, Alternatives, Costs to

## Participants, Payment to Participants, Confidentiality, Right to Withdraw, & University Statement

### Which Consent Form Template should you use?

1. **Sponsor's Template** - If your study already has a sponsored consent template, you can use your sponsor's template and incorporate UMB standard language including the applicable University Statement.
2. **Consent Form Template** – This template should be used as a guide for all research studies including parental consent forms and LAR consent forms. [\*\*CLICK HERE TO DOWNLOAD A CONSENT FORM TEMPLATE\*\*](#)
3. **Assent Form Template** – This template should be used to assent participants ages 13-17 and if applicable to your study - cognitively impaired participants. [\*\*CLICK HERE TO DOWNLOAD AN ASSENT FORM TEMPLATE\*\*](#)
4. **VA Consent Form Template** – This template should be used if your study is being conducted at the Baltimore VA. [\*\*CLICK HERE TO DOWNLOAD A VA CONSENT FORM TEMPLATE\*\*](#)
5. **HIPAA Authorization Form (all uses)**

The following basic elements of informed consent are required to be disclosed in all research consent forms pursuant to 45 CFR 46(a-b):

#### (a) Basic elements of informed consent.

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, including the possibility that the Food and Drug Administration (FDA) may inspect the records if applicable;
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an

explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

ID: VIEW43E6DF60D5400  
Name: Consent Forms - Draft

View: Additional Documents

## Additional Documents

### 1 Upload all additional documents here: [\(Uploading Help\)](#)

Name	Created	Modified Date
<a href="#">HIPAA Form</a>	4/7/2009 9:43 AM	4/7/2009 9:43 AM
<a href="#">LAR Documentation</a>	4/7/2009 10:09 AM	4/7/2009 10:09 AM
<a href="#">LAR Initial Interview</a>	10/29/2009 1:10 PM	10/29/2009 1:10 PM
<a href="#">Letter to Potential Participants</a>	8/13/2010 4:22 PM	8/13/2010 4:22 PM
<a href="#">MRI Clearance Form</a>	5/18/2010 3:30 PM	5/18/2010 3:30 PM
<a href="#">MRI Safety Screen</a>	11/8/2010 11:41 AM	11/8/2010 11:41 AM
<a href="#">Participant Letter</a>	12/4/2009 5:40 PM	12/4/2009 5:40 PM

Name  
Patient Initial Interview

Created  
10/29/2009 1:09 PM

Modified Date  
10/29/2009 1:09 PM

ID: VIEW43E9519AA4800  
Name: Additional Documents

View: Final Page of IRB Protocol

## Final Page of Application

**You have reached the final page of this application.** It is recommended that you click on the "Hide/Show Errors" link on the upper or lower breadcrumb row of this page. The "Hide/Show Errors" will do a search of your application, and highlight areas that are required or need to be completed prior to submitting.

By submitting this application, the investigator attests to the fact that all research activity to be implemented in human subjects is completely and accurately described herein. By submitting this application, you are electronically routing the protocol for departmental scientific review and all other necessary reviews. According to information you have provided, this application will need signature(s) of the following Department Chairs before it can be sent to the Human Research Protections Office and to the IRB for review. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization  
Diagnostic Radiology

Review Status  
Complete

**Required Safety Committee Reviews** - In addition to the IRB, the following committees must review this submission. Each additional committee has a separate online form that the study team will be required to fill out. All committee applications (IRB plus those listed here) must be completed properly before the 'package' of applications can be submitted. The team may complete these additional forms in any order or at any time prior to submission of the IRB Application. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's Workspace.

Name of Related Submission

*This protocol has no related submissions (RSC, GCRC, IBC, etc)*

You may check the progress of your application at any time by returning to the Workspace of this submission. A detailed history, including notes, dates, and times of events, is provided to you for this purpose.

If a reviewer returns the application to you unsigned, you must address their concerns and resubmit the protocol for signature to all designated departments. After all signees have reviewed the application, it will automatically be sent to the Human Research Protections Office for placement on the next available IRB agenda. By submitting this application, you are certifying that this submission conforms with the OSHA/HHS guidelines for HIV/HBV occupational safety. Please know that once an application has been put on the IRB agenda, no further changes to the application can take place until after IRB review and approval. Changes made to the submission after its approval are to be considered amendments.

**Click the "Finish" button.**

ID: VIEW43E6EA11B5400  
Name: Final Page of IRB Protocol



## Disruption of Default Mode Network following Mild Traumatic Brain Injury

C. Sours<sup>1</sup>, J. Betz<sup>1</sup>, S. Roys<sup>1</sup>, B. Aarabi<sup>2</sup>, K. Shanmuganathan<sup>2</sup>, J. Greenspan<sup>3</sup>, and R. Gullapalli<sup>1,4</sup>

<sup>1</sup>Core for Translational Research in Imaging @ Maryland (CTRIM), University of Maryland School of Medicine, Baltimore, Maryland, United States, <sup>2</sup>University of Maryland School of Medicine, Baltimore, MD, United States, <sup>3</sup>Department of Biomedical Sciences and Program in Neuroscience, University of Maryland School of Dentistry, Baltimore, Maryland, United States, <sup>4</sup>Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine, Baltimore, Maryland, United States

### Introduction

The default mode network (DMN) is a network of regions consistently found to be deactivated during task related activities while remaining active during rest (2). The network includes lateral parietal cortex, posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), medial temporal lobe (MTL), and medial frontal cortex. This network has been found to be disrupted in multiple patient populations with cognitive deficits including Alzheimer's (3) and schizophrenia (1). Furthermore, functional connectivity within the network has been correlated to performance on working memory tasks in healthy controls (4). Due to the diffuse axonal injuries and cognitive deficits associated with mild traumatic brain injury (TBI), we hypothesize that the functional connectivity within the DMN will be decreased during the acute stage in individuals suffering from mild TBI.

### Methods

Resting state MRI data was obtained on patients suffering from mild TBI within ten days of initial injury (N=16; avg 3 days) and again one month following initial injury (N=6; avg 39 days). All imaging was performed on a Siemens 3T MRI scanner using an 12-channel receive only head coil. T2\*-weighted images were acquired using a single-shot EPI sequence (TE = 30 ms, TR = 2000 ms, FOV = 220 mm, resolution = 64 × 64) with 24 axial slices (sl. thick. = 6 mm) over 6 min 42 s that yielded 171 time points. A high resolution T1-weighted-MPRAGE (TE = 3.44 ms, TR = 2250ms, TI = 900ms, flip angle = 9°, resolution = 256 × 256 × 96, FOV = 22 cm, sl. Thick. = 1.5 mm) was also acquired for anatomic reference. Data were analyzed using AFNI (Robert Cox, NIH) and MATLAB (MathWorks Inc., Natick, MA). Each subject's functional images were corrected for slice timing, optionally filtered to remove physiological artifacts, and registered to the first volume of the functional scan. A 6mm FWHM Gaussian blur was applied to the registered functional scans. Five mm ROI spheres were made in the posterior cingulate cortex (PCC) in original space and the average time series was correlated with every voxel in the brain to create an individual whole brain correlation map. These whole brain correlation maps along with the T1-MPRAGE images for each individual were transformed to Talairach space. Whole brain correlation maps were converted to Z-scores using the Fisher transformation and t-tests were run on the data to create a group correlation map which was then transformed to correlation coefficients and thresholded at  $r = \pm 0.500$ . In addition average correlation coefficients between a 5mm temporal ROI from the PCC and 5mm ROI spheres in the bilateral MTL, frontal, thalamus, parietal and medial ACC were computed. These values were used as a measure of the strength of functional connectivity. The same analysis was run on a control group (N=7) which was compared to the results of the TBI groups.

### Results and Discussion

Figure 1: Group Correlation Maps

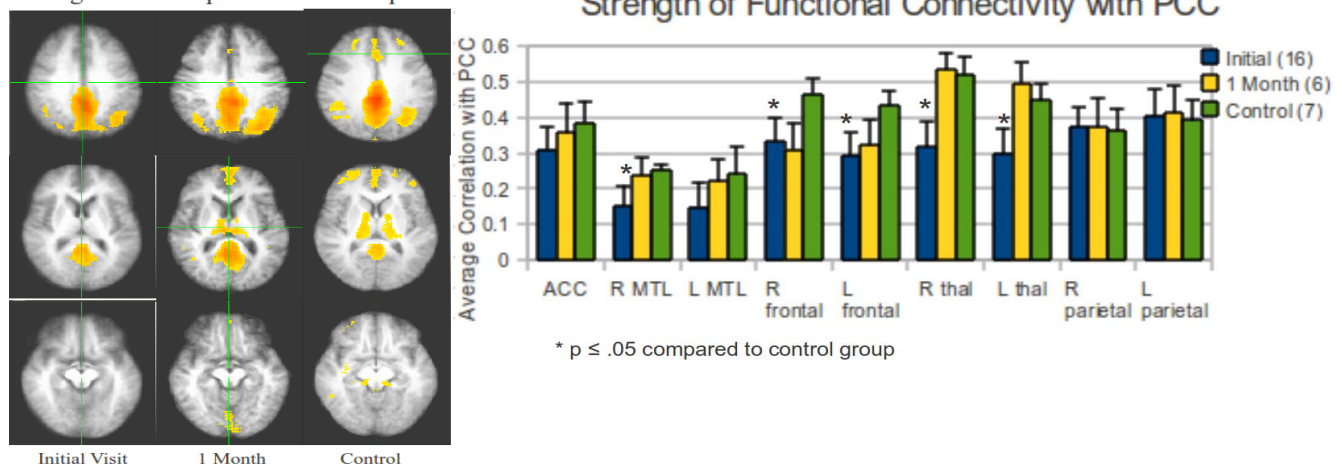


Figure 1 shows the group maps between the control subjects and the mild TBI patients during their initial visit and four week visit following mild TBI. Based on our ROI analysis (as shown in the histograms above), we observe a significant decrease in functional connectivity among the mild TBI patients during their initial visit in the right MTL ( $p=.036$ ), right frontal ( $p=.027$ ), left frontal ( $p=.020$ ), right thalamus ( $p=.006$ ), and left thalamus ( $p=.026$ ) compared to controls. Very little effect was seen in the bilateral posterior parietal areas (right:  $p=.428$ ; left:  $p=.431$ ) and ACC ( $p=.153$ ) among the mild TBI patients. The DMN begins to show signs of normalization after one month with increased functional connectivity in the bilateral thalamus, and right MTL and left frontal compared to the initial visit. However, there remains a decrease in functional connectivity in the right frontal cortex compared to controls at one month ( $p=.041$ ). This normalization to the normal control values at the four week time point can be visualized in the group correlation maps shown in Figure 1.

### Conclusion

Functional connectivity within the DMN is disrupted initially following mild TBI with decreased functional connectivity in the bilateral frontal cortex, right MTL, and bilateral thalamus. This disruption began to normalize at one month with the functional connectivity approaching that of the controls in the thalamus, right MTL, left frontal but still showing decreased functional connectivity within the right frontal cortex. The frontal cortex is involved in executive function and working memory which are common deficits of mild TBI. We believe that this longitudinal analysis of functional connectivity within the resting state helps to explain some of the cognitive deficits associated with mild TBI that persist for over one month after the initial injury.

### References

(1) Garrity et al. American Journal of Psychiatry. 2007;164(3):450–457. (2) Greicius et al. PNAS. 2003;100:253–258. (3) Greicius et al. PNAS. 2004;101: 4637–4642. (4) Wang et al. Neuroimage. 2010;51(2):910-917.



# Reliability of functional and effective connectivity of the resting state motor network in healthy subjects

T. Kavallappa<sup>1</sup>, S. Roys<sup>2</sup>, A. Roy<sup>3</sup>, J. Greenspan<sup>2</sup>, R. Gullapalli<sup>2</sup>, and A. McMillan<sup>2</sup>

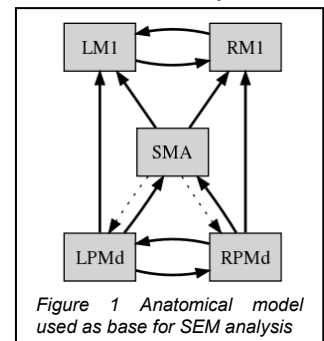
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**Introduction:** Resting state functional connectivity of the cortical motor network has been shown to be reliable and consistent; however, the same has not been shown for measurements of effective connectivity. In this study, we use structural equation modeling (SEM), a frequently used method to evaluate effective connectivity, to evaluate reliability of these measurements in the human resting state motor network. Because connectivity measurements have shown sensitivity to physiological noise, we performed our reliability assessment using four different filtering methods. The filtering methods used were i) Standard preprocessing with no physiological filtering ii) retrospective correction of physiological effects using RETROICOR iii) White matter + CSF mean signal filtering and iv) whole brain mean signal filtered data.

**Methods:** Multiple resting state data sets were obtained from 7 healthy right-handed subjects during three separate sessions spanning over two months using a Siemens Tim-Trio 3T scanner. During each of the 3 sessions, three resting state scans were obtained using a single-shot EPI acquisition with 24 axial slices (TE = 30ms, TR = 2s, FOV = 22cm, slice thickness = 6mm with no gap), yielding 171 time points in 342s. Respiratory data was acquired during scanning via a nasal cannula at a sampling rate of 500Hz. Standard data preprocessing included slice timing correction, spatial registration, linear detrending, and spatial smoothing using a 6mm FWHM Gaussian blur. 3D structural brain images were automatically segmented into gray matter (GM), white matter (WM) and CSF component images which were used to extract average GM, WM and CSF time series from the resting state scans. Further processing of the data was performed to yield separate data sets that included (i) Preprocessed data with no physiological filtering (ii) Respiratory noise filtered from the data using retrospective image correction (RETROICOR), (iii) White matter + CSF mean signal filtered data where the average time series of white matter and CSF (WM-CSF) was regressed from individual voxels, since the WM-CSF signals are expected to be independent of the BOLD signal fluctuations present in the gray matter, and (iv) Global mean brain signal filtered data where the average time series from all brain voxels (GM+WM+CSF) was regressed from each individual voxel time series. In this analysis the local signal changes are of interest, and the global signal is assumed to represent non-neuronal noise. Five ROI's were chosen as part of the resting state motor network in the cortex: left & right primary motor areas (LM1, RM1), dorsal premotor areas (LPMd, RPMd), and the supplementary motor area (SMA). After preprocessing, LM1 was chosen as seed region using data from the motor paradigm to obtain functional connectivity maps. Spherical ROIs (radius ranging from 7-13 mm) were manually drawn in the LM1, RM1, RPMd, LPMd, and SMA using calculated functional connectivity maps as a guide. Group correlation matrices were obtained from the concatenated ROI time series (for all subjects and sessions). The correlation coefficients, along with an initial causal model (Fig 1) were used as input to SEM. The SEM package in R was used to test and refine the causal model for the resting state motor network using modification indices and goodness-of-fit indices (we define RMSEA<0.05, AGFI>0.99 as a good model fit). A resampling test was performed to examine the reliability of the model, and determine the distribution of the path coefficients using different combinations of the subjects' data. In the resampling test the path coefficients were determined for combinations of pooled data from all 7 subjects, taken 6 subjects at a time, to assess group functional and effective connectivity.

**Results and Discussion:** The initial anatomical model for the resting state network is shown in Figure 1 with bold and dotted arrows. Using modification indices in R, the model that demonstrated the best fit to the data (for all four filtering methods) included all of the connections from the anatomical model except connections from SMA to the bilateral dorsal premotor areas. This model is shown in solid lines in Figure 1. The resting state motor network obtained demonstrates reciprocal connections across bilateral primary motor areas, and the premotor areas. The model follows a symmetric structure with the premotor areas influencing the SMA and the ipsilateral primary motor areas. The SMA influences both the primary motor areas. Coefficient of variation was calculated for each connection at combination level 6 (7 different combinations). While functional connectivity was more consistent across the 4 filtering methods used (COV <= 0.08) as shown in Table 1, it was not so with effective connectivity (Table 2). Although the model yielded a good fit for all the filtering methods, the path coefficients were only stable for certain connections (e.g variability of LM1->RM1 path coefficients greater than RPMd->RM1). The correlation coefficients from the RETROICOR filtered dataset and the dataset with no physiological filtering had higher path coefficients, and lower variability, than that of the global mean signal regressed and WM-CSF mean signal regressed datasets. The path coefficients, in general, displayed higher variability for the WM-CSF and the global mean filtered datasets.

**Conclusion:** It is seen that while a single causal model fit all the datasets considered, the path coefficients demonstrated high degree of variability. The variability of both functional connectivity and effective connectivity was less for the physiologically filtered dataset and the dataset with no filtering, compared to the WM-CSF and global mean filtered datasets. Given the variability of effective connectivity from SEM, interpretation of such data should be treated with caution.



Correlation Coefficients				
Connections	I	II	III	IV
LM1 – LPMd	0.70	0.72	0.47	0.44
LM1 – RM1	0.80	0.81	0.67	0.60
LM1 – RPMd	0.64	0.66	0.42	0.37
LM1 – SMA	0.74	0.75	0.52	0.43
LPMd – RM1	0.64	0.67	0.41	0.36
LPMd – RPMd	0.72	0.78	0.61	0.57
LPMd – SMA	0.67	0.68	0.38	0.35
RM1 – RPMd	0.70	0.74	0.55	0.51
RM1 – SMA	0.76	0.76	0.55	0.47
RPMd – SMA	0.63	0.67	0.39	0.33

Table 1: Correlation coefficients for all subjects for the 4 filtering methods (Mean (sd)) at combination level 6 [COV<0.03, 0.03<COV<0.1]

Path Coefficients				
Connections	I	II	III	IV
LM1 → RM1	0.14 (0.07)	0.16 (0.07)	0.20 (0.08)	0.14 (0.06)
RM1 → LM1	0.38 (0.05)	0.35 (0.04)	0.33 (0.05)	0.34 (0.04)
RPMd → LPMd	0.43 (0.02)	0.48 (0.01)	0.34 (0.02)	0.32 (0.02)
LPMd → RPMd	0.43 (0.02)	0.48 (0.01)	0.34 (0.02)	0.32 (0.02)
LPMd → LM1	0.27 (0.02)	0.29 (0.02)	0.24 (0.02)	0.25 (0.02)
RPMd → RM1	0.31 (0.03)	0.37 (0.04)	0.34 (0.03)	0.36 (0.03)
LPMd → SMA	0.44 (0.03)	0.41 (0.02)	0.23 (0.04)	0.23 (0.04)
RPMd → SMA	0.31 (0.03)	0.35 (0.02)	0.25 (0.03)	0.19 (0.03)
SMA → RM1	0.46 (0.05)	0.39 (0.03)	0.32 (0.04)	0.29 (0.03)
SMA → LM1	0.27 (0.03)	0.28 (0.03)	0.25 (0.02)	0.18 (0.02)

Table 2: Path coefficients of the final causal model (Mean (sd)) at combination level 6 [0.03<COV<0.1, 0.1<COV<0.2, COV>0.2]

**References:** [1] Gonzalez-Lima ARMF, Human Brain Mapping 2 (1-2) (1994) 2–22. [2] Fox J, With the SEM Package in R, Structural Equation Modeling 13 (3) (2006) 465–486. [3] Zhuang J, LaConte S, Peltier S, Zhang K, Hu X, Neuroimage 25 (2) (2005) 462–470.

# Disruption of the Functional Connectivity Following Mild Traumatic Brain Injury

C. Sours, J. Betz, S. Roys, B. Aarabi, K. Shanmuganathan, J. Greenspan, and R. Gullapalli

## Introduction

The default mode network (DMN) is a network of regions found to be deactivated during task related activities but active during rest (1,2). Functional connectivity within the network has been correlated with performance on working memory tasks in healthy controls (4,5) and has been shown to be disrupted in patients with Alzheimer's disease, a disorder with pronounced cognitive impairments (3). Due to the cognitive deficits associated with mild traumatic brain injury (mTBI), we hypothesize that the functional connectivity within the DMN will be decreased during the acute and sub-acute stages of mTBI.

## Methods

Resting state data was obtained within 10 days of injury (avg 4 days) in 15 mTBI patients (avg GCS=14.8) and at approximately one month (avg 43 days) in 8 mTBI patients (avg GCS=14.6) as well as 7 controls. Data were analyzed using AFNI (Robert Cox, NIH) and MATLAB (MathWorks Inc., Natick, MA). Each subject's functional images were corrected for slice timing, optimally filtered to remove physiological artifacts, registered to the first volume of the functional scan, and a 6mm FWHM Gaussian blur was applied.

Imaging was performed on a Siemens 3T MRI scanner using a 12-channel receive only head coil. T2\*-weighted images were acquired using a single-shot EPI sequence (TE=30 ms, TR=2000 ms, FOV=220 mm, resolution =64×64) with 24 axial slices (sl. thick. =6 mm) over 6 min 42 s that yielded 171 time points. A high resolution T1-weighted-MPRAGE (TE=3.44 ms, TR=2250ms, TI=900ms, flip angle =9°, resolution = 256×256×96, FOV = 22 cm, sl. Thick. =1.5 mm) was also acquired for anatomic reference. For each subject 5mm ROI spheres were made in the posterior cingulate cortex (PCC) and the average time series of the ROI spheres was used as a reference time series which was correlated with every voxel in the brain within the resting state scan. This whole brain correlation map was transformed to Talairach space and converted to Z-scores using Fisher's transformation. Voxel based t-tests were run on the data to create a group correlation map which was then transformed to correlation coefficients and thresholded at  $r = \pm 0.500$ .

In addition, average correlation coefficients between a 5mm temporal ROI from the PCC and 5mm ROI spheres in the bilateral medial temporal lobes (MTL), medial frontal, thalamus, parietal and medial anterior cingulate cortex (ACC) were computed. These values were used as a measure of the strength of functional connectivity.

## Results

Figure 1 shows the group correlation maps of the PCC seed in control subjects compared to the acute and sub-acute mTBI patients. There is decreased functional connectivity in the frontal lobes, thalamus, and MTL in the mTBI patients. This observation is supported by our ROI analysis shown in Figure 2. We observe decreased functional connectivity among the mTBI patients in the R MTL ( $p=.0027$ ), R frontal ( $p=.0158$ ), L frontal ( $p=.0147$ ), R thalamus ( $p=.0019$ ) and L thalamus ( $p=.0080$ ), but not in the medial ACC, L MTL, or bilateral parietal. At the sub-acute stage, this decreased functional connectivity remains in the L frontal ( $p=.0085$ ) and R frontal ( $p=.0219$ ) areas but appears to normalize to controls in the R MTL and bilateral thalamus. Results of all Student's t tests are shown in Figure 3.

## Conclusion

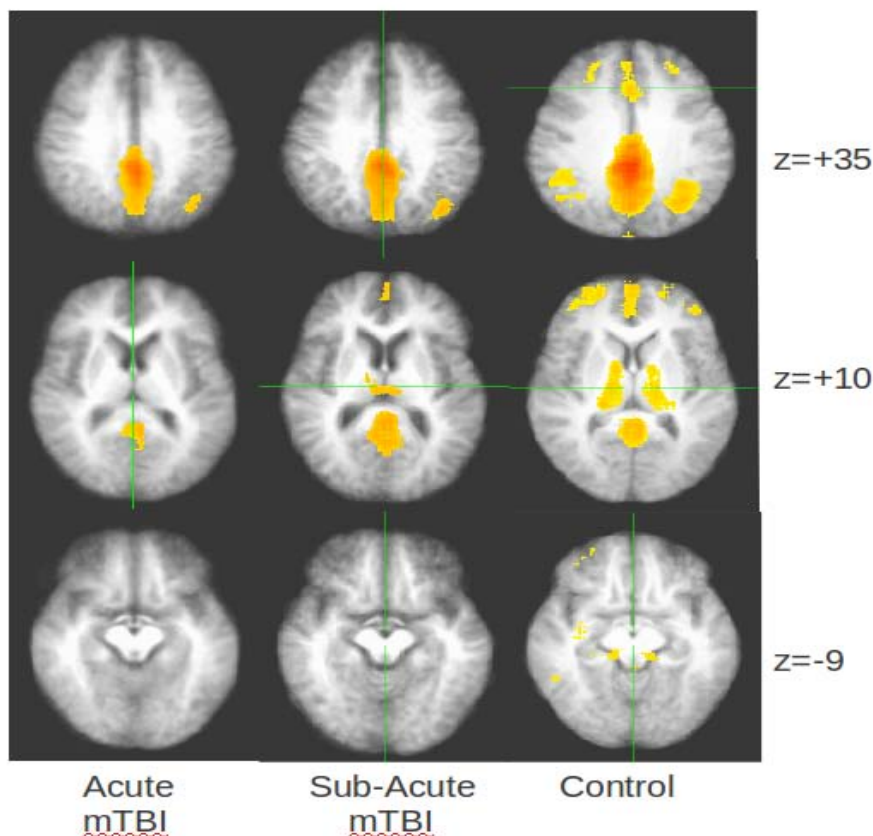
Functional connectivity within the DMN is disrupted in the acute stage of mTBI in the right MTL, bilateral medial frontal area and bilateral thalamus. In the sub-acute stage, functional

connectivity remains decreased only in the bilateral frontal areas while it appears to normalize in the right MTL and bilateral thalamus. We believe that the continued disruption of the DMN within the frontal lobes helps to explain some of the cognitive deficits associated with mTBI that are often left unexplained by classical structural scans. This disruption is indicative of reduced neural connections and is likely caused by the diffuse axonal injury (DAI) often seen in these mTBI patients.

## References

- (1) Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C. (2005), 'The human brain intrinsically organized into dynamic, anticorrelated functional networks', PNAS, vol. 102, no. 27, pp. 9673-9678.
- (2) Greicius, M.D. Krasnow, B., Reiss, A.L., Menon, V. (2003), 'Functional connectivity in the resting brain: A network analysis of the default mode hypothesis', PNAS, vol. 100, pp. 253–258.
- (3) Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V. (2004), 'Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI', PNAS, vol. 101, pp. 4637–4642.
- (4) Hampson, M., Driesen, N.R., Skudlarski, P., Gore, J.C., Constable, R.T. (2006), 'Brain connectivity related to working memory performance', The Journal of Neuroscience, vol 26, no. 51, pp. 13338-13343.
- (5) Wang, L., LaViolette, P., O'Keefe, K., Putcha, D., Bakkour, A., Van Dijk, K.R., Pihlajamaki, M., Dickerson, B.C., Sperling, R.A. (2010), 'Intrinsic connectivity between the hippocampus and posteromedial cortex predicts memory performance in cognitively intact older individuals', Neuroimage, vol. 51, no. 2, pp. 910-917.

Figure 1: Group Maps of Correlation with PCC  
Thresholded at  $r=.50$



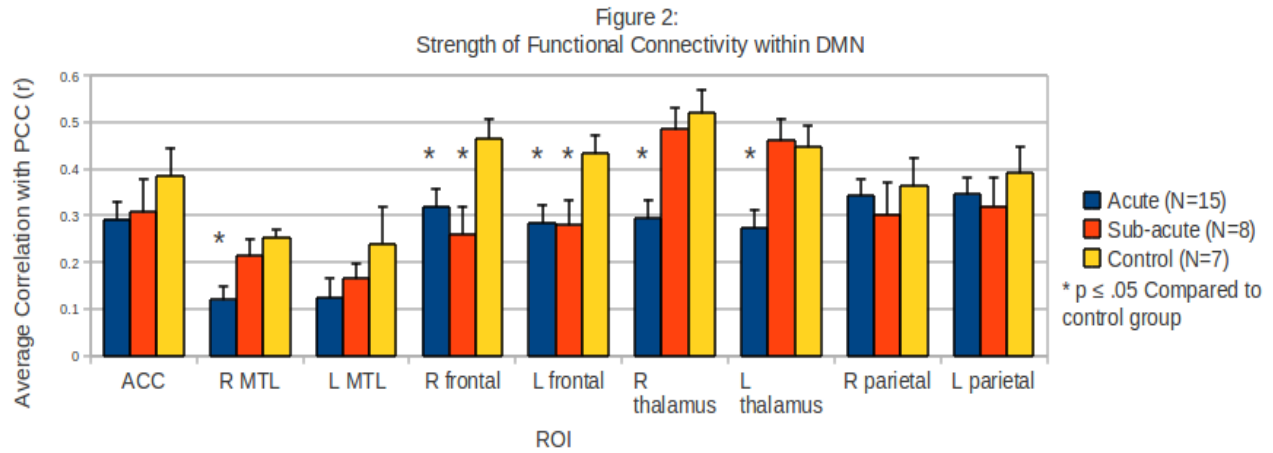


Figure 3: Results of T-tests for ROIs  
(P values)

	ACC	R MTL	L MTL	R frontal	L frontal	R thalamus	L thalamus	R parietal	L parietal
Acute vs control	0.0969	<b>0.0027</b>	0.0789	<b>0.0158</b>	<b>0.0147</b>	<b>0.0019</b>	<b>0.0080</b>	0.3758	0.2410
Acute vs Sub-acute	0.4194	<b>0.0293</b>	0.2550	0.2004	0.4720	<b>0.0040</b>	<b>0.0043</b>	0.2803	0.3506
Sub-acute vs Control	0.2080	0.1683	0.1840	<b>0.0085</b>	<b>0.0219</b>	0.3059	0.4194	0.2616	0.2105



# Functional Connectivity following Mild TBI-Preliminary Results from MagNeT Study (Magnetic Resonance Imaging of NeuroTraumaStudy)

**Chandler Sours**

University of Maryland School of Medicine

Core for Translational Imaging @ Maryland (CTRIM)

Departments of Neuroscience & Diagnostic Radiology

DOD award # W81XWH-08-1-0725, PT 075827



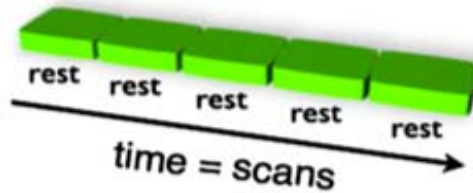
# MagNeTS-Advanced Neuroimaging

- Majority of people who sustain mTBI have no evidence of injury based on structural CT or MRI
  - However many of these individuals still suffer post concussive symptoms
- Advanced neuroimaging techniques need to be investigated in order to better characterize the effect of mTBI on the brain
- These techniques include
  - fMRI
    - Resting state fMRI
  - Diffusion tensor imaging (DTI)
  - Diffusion kurtosis imaging (DKI)
  - H1-Magnetic resonance spectroscopy (MRS)
  - Arterial spin labeling

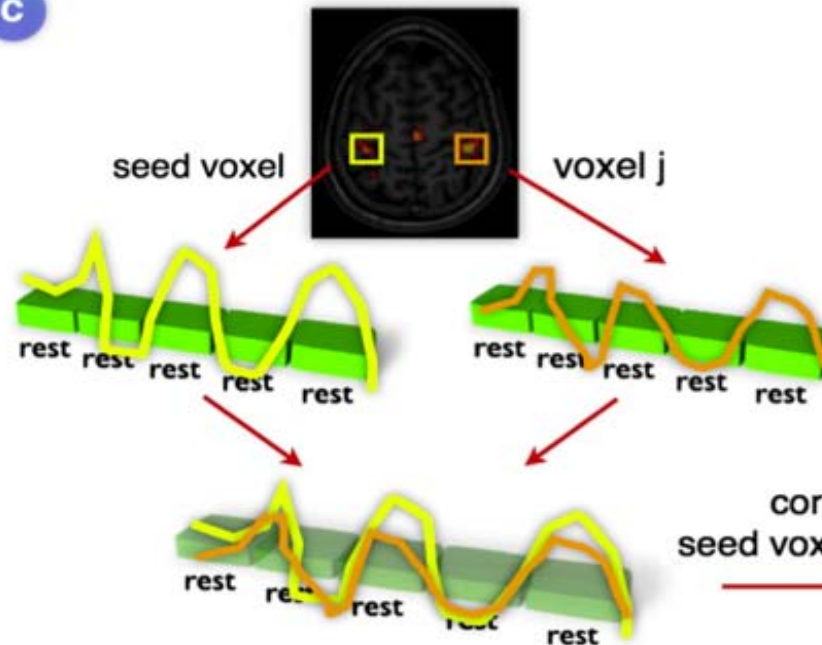
# Resting state Functional Connectivity

resting-state fMRI

a

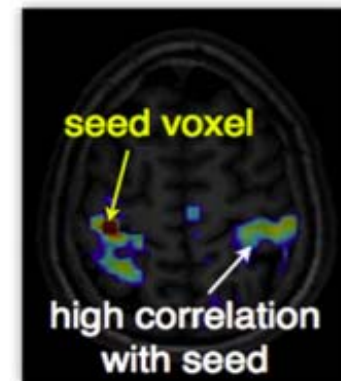


c



d

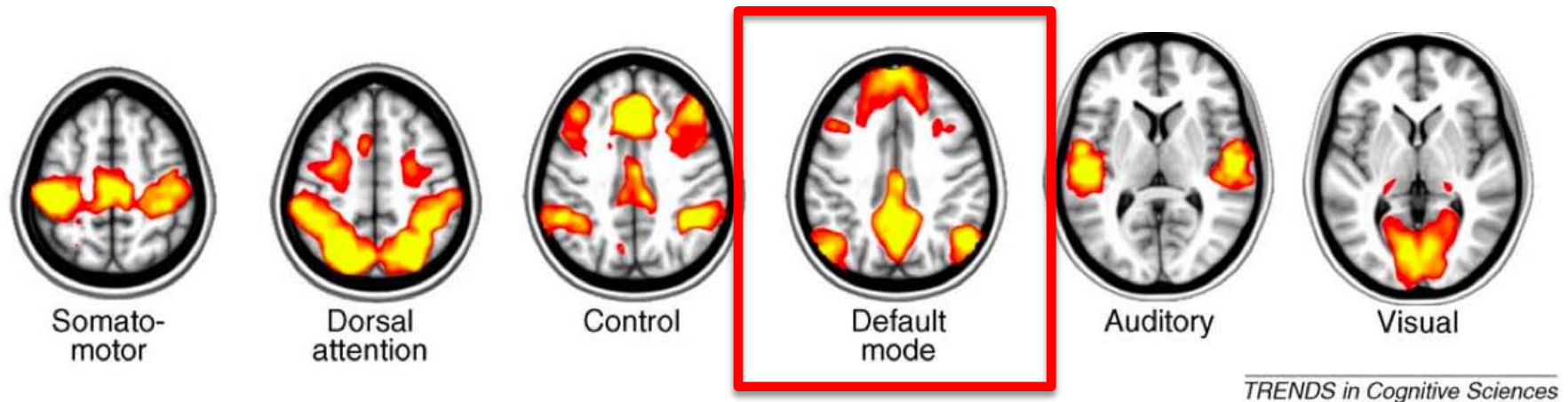
functional connectivity map





# Resting State Functional Connectivity

- Defined as “the temporal correlation of a neurophysiological index measured in different brain areas” -Karl Friston (1993)
- Measures how well different brain regions are working together not if they are structurally connected

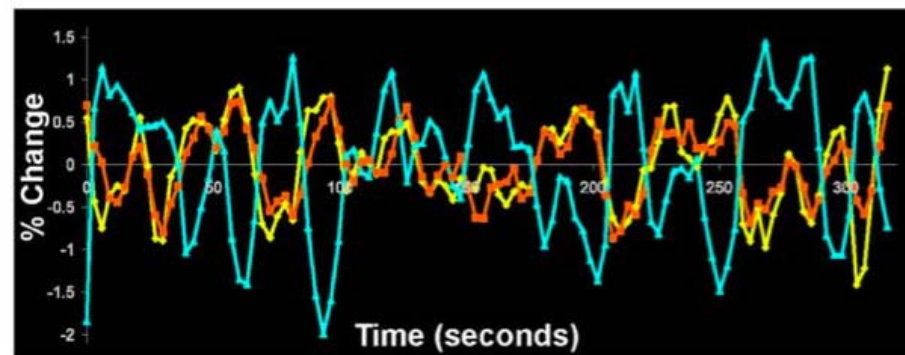
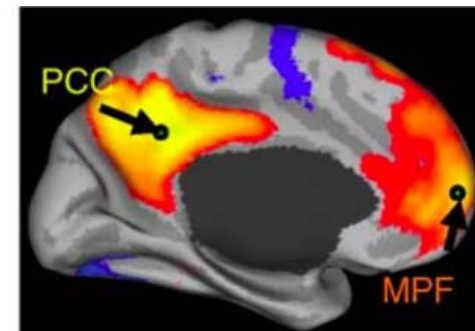
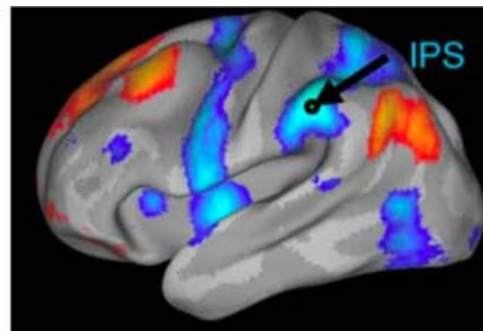


## Resting State Networks



# Default Mode Network (DMN)

- Thought to be involved in episodic memory, internal thoughts, meditation
- Deactivated during goal directed behavior while more active during rest
- Interplay between Dorsal Attention Network (aka task positive network) and DMN (aka task negative network)



# DMN and TBI

- **Severe TBI**
  - Decreased interhemispheric functional connectivity in hippocampus and ACC (Marquez de la Plata et al 2011)
- **Sports related TBI**
  - Decreased interhemispheric functional connectivity in hippocampus, visual cortex, and DLPFC (Slobounov et al 2011)
- **Mild TBI**
  - Decreased functional connectivity within DMN in semiacute and chronic stages (Mayer et al 2011)

# Participants



- Controls
  - N=15 (31.8 yrs +/-9.4), 5F)
- Acute stage (within 10 days of injury)
  - N=26 (44.0yrs +/-16.7, 6F)
- Sub-acute stage (approximately 30 days after injury)
  - N=15 (49.8+/-18.7, 6F)
- All recruited from R Adams Cowley Shock Trauma center
  - Admission GCS 13-15, and LOC and/or PTA

# Methods

- **Resting state fMRI scan**
  - Seed based correlation method
  - 5mm spherical ROI in the posterior cingulate cortex
- **ANAM-Automated Neuropsychological Assessment Metrics**
- **Tests includes**
  - Code substitution - processing speed
  - Code substitution delayed - short term memory
  - Match to sample - working memory
  - Procedural reaction time - processing speed
  - Mathematical processing
  - Simple reaction time (x2)



# Results from Functional Connectivity Analysis -Case Studies



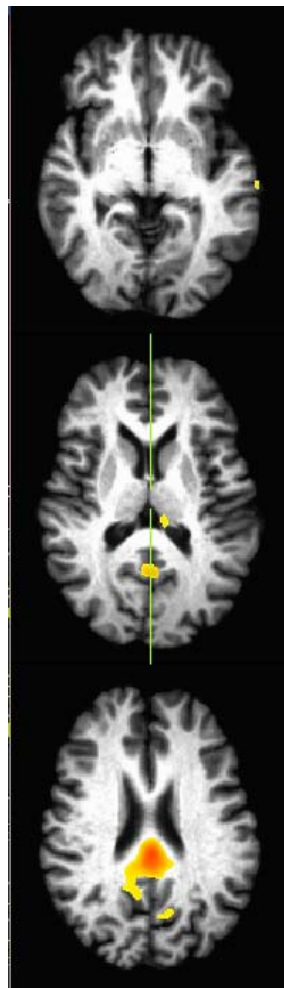
# Quick Case Studies

- Patient A
- 49 year old Female
- GCS 15
- Fall
- Negative Head CT
- Reaction Time on ANAM increased
- Score on Rivermead Symptoms:
  - Initial = 39
  - 1 month = 34

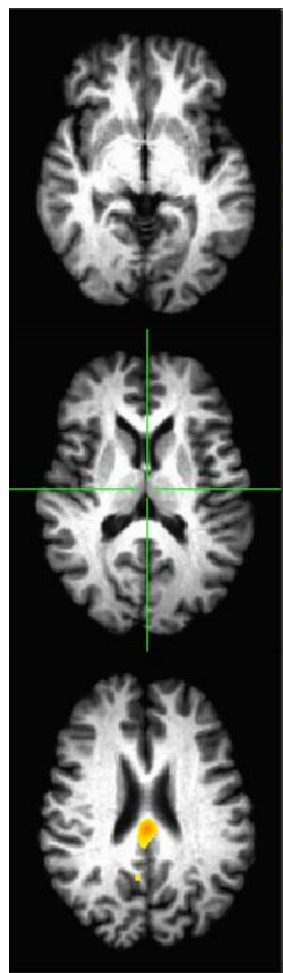
- Patient B
- 20 year old Male
- GCS 15
- Assault
- Positive Head CT
- Reaction Time on ANAM comparable to controls
- Score on Rivermead Symptoms:
  - Initial = 1
  - 1 month = 1

# DMN Functional Connectivity

- Patient A

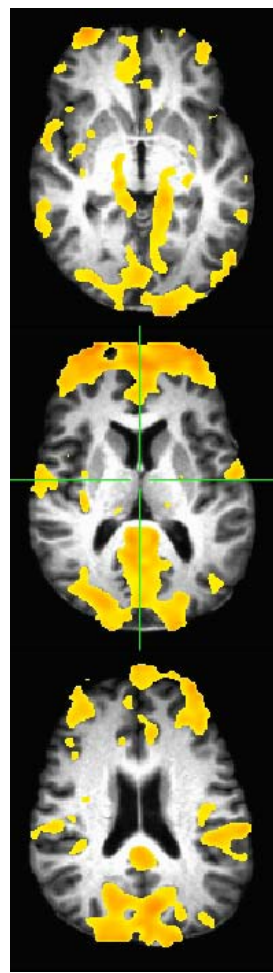


Initial Visit

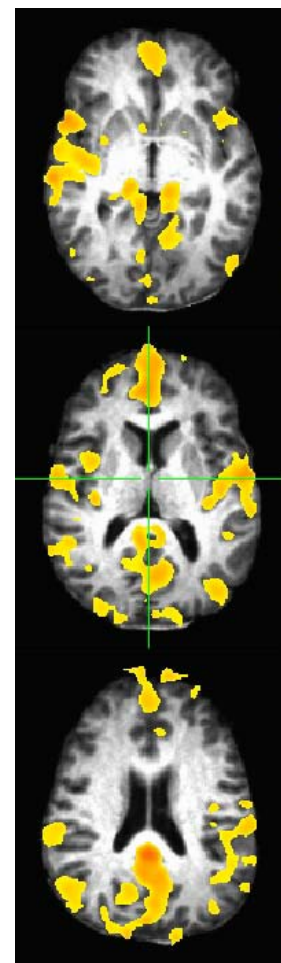


1 month

- Patient B



Initial Visit



1 month

Thresholded ( $r \pm 0.500$ )



# Results from Functional Connectivity Analysis -Group Analysis



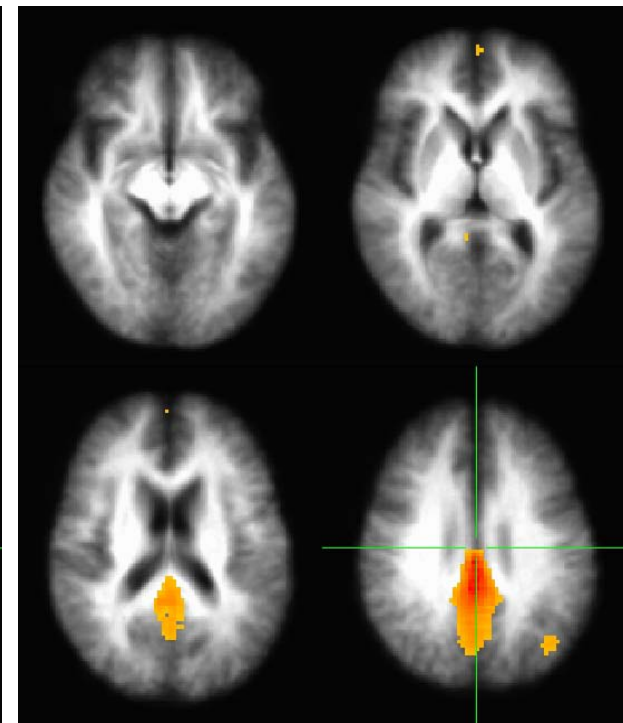
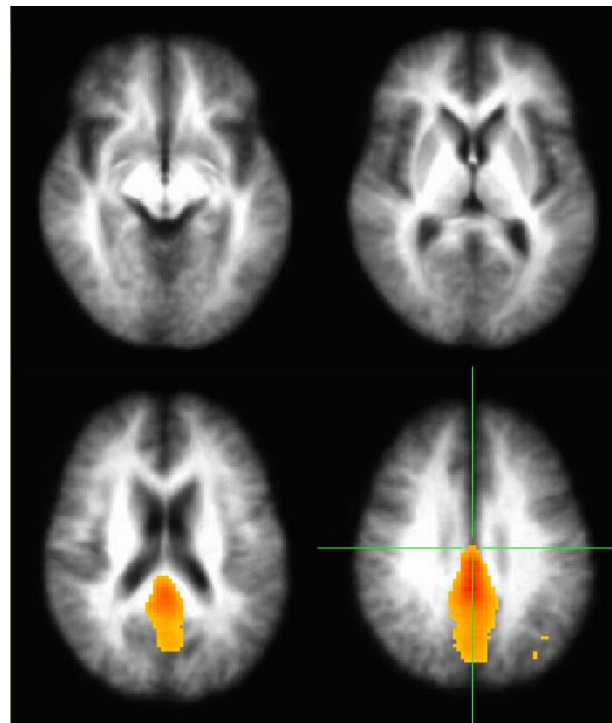
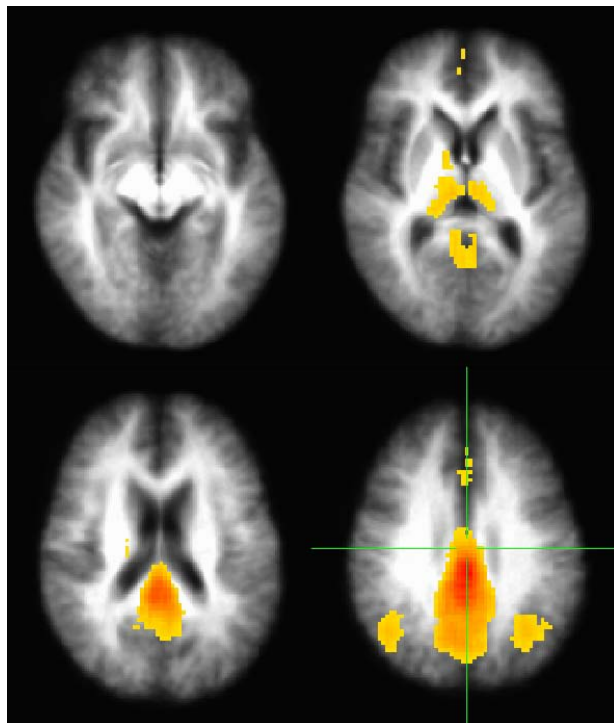


# Default Mode Network-Group

Control

Acute

Sub-acute

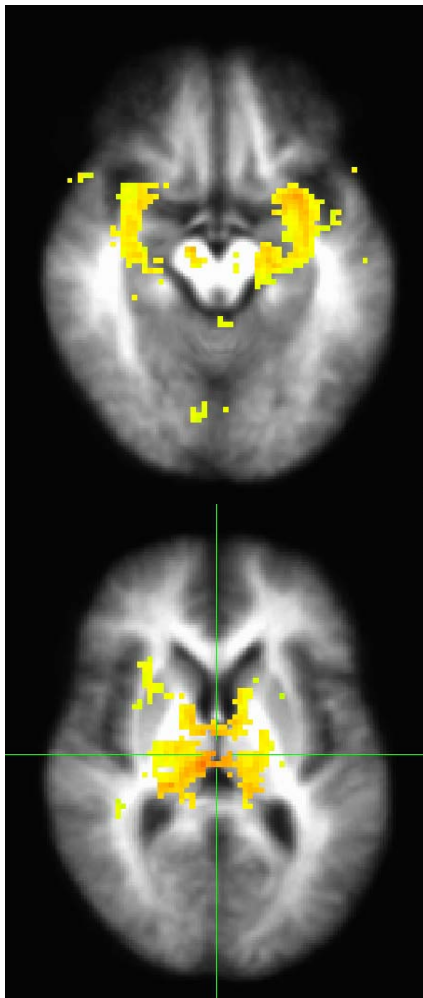


PCC Group Correlation Maps ( $r \pm 0.500$ )

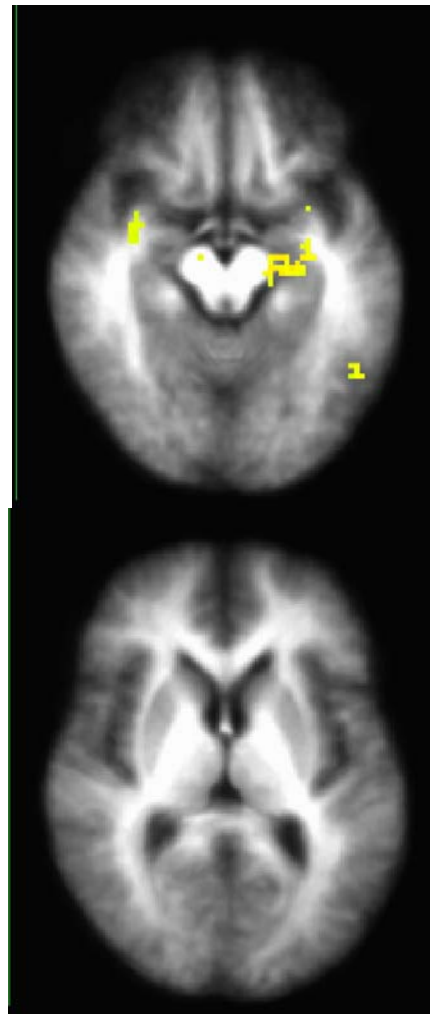


# Default Mode Network-Group Comparison

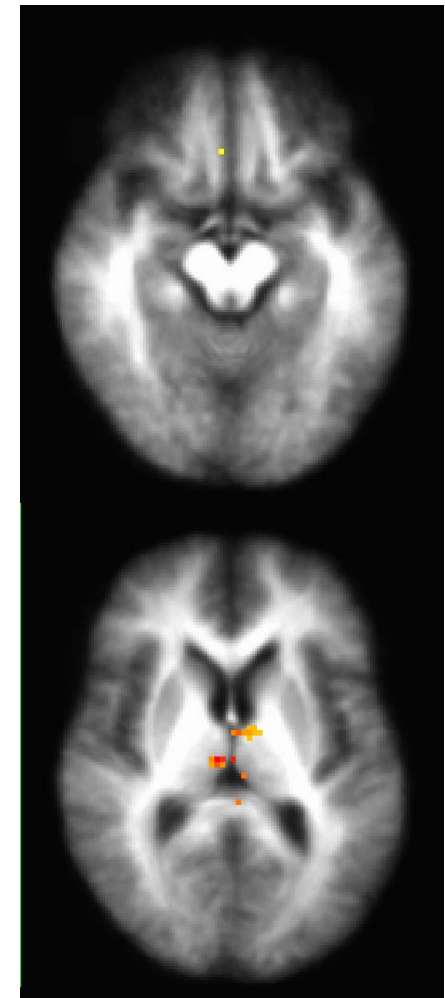
Acute vs Control



Sub-acute vs Control

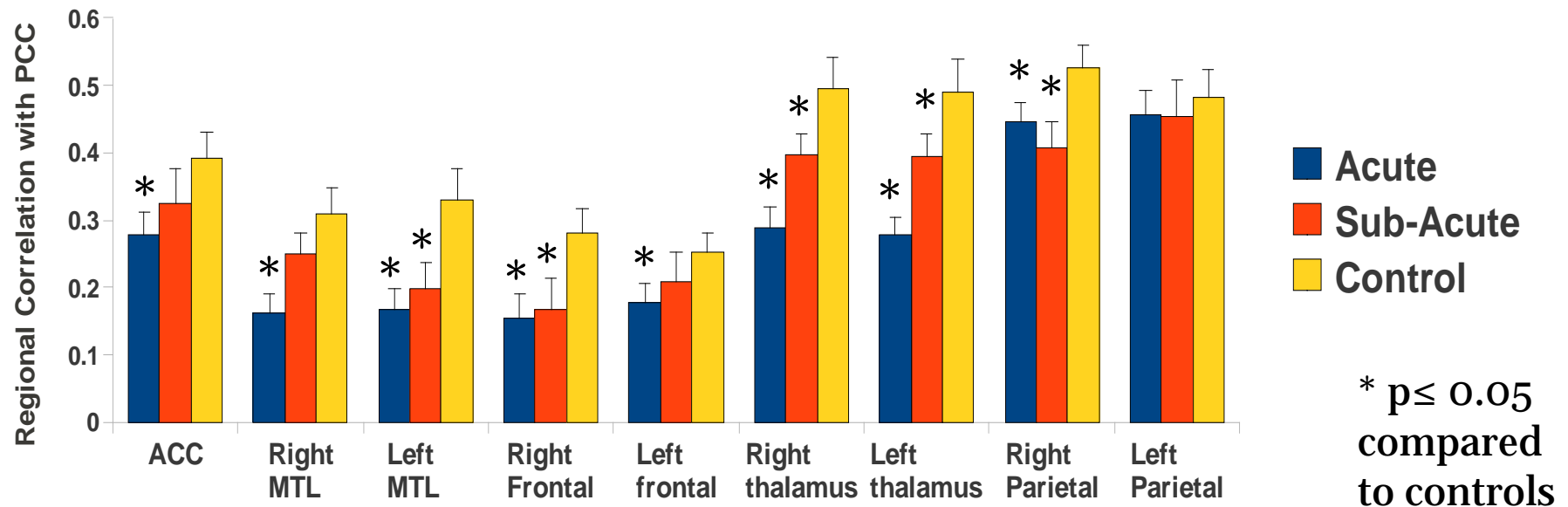


Sub-acute vs Acute



( $P < 0.001$ , uncorrected)

## Strength of Functional Connectivity within DMN



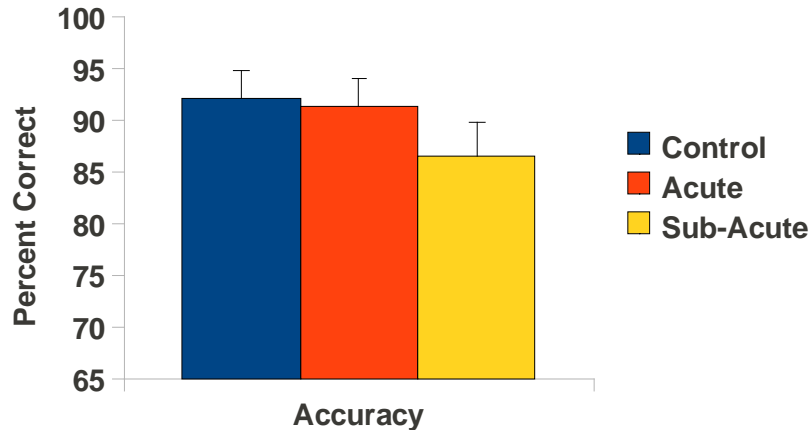
- Reduced functional connectivity during the Acute Stage
  - ACC
  - Bilateral MTL
  - Bilateral Thalamus
  - Right Frontal
  - Right Parietal
- Reduced functional connectivity during the Sub-acute Stage
  - Left MTL
  - Bilateral Thalamus
  - Right Frontal
  - Right Parietal



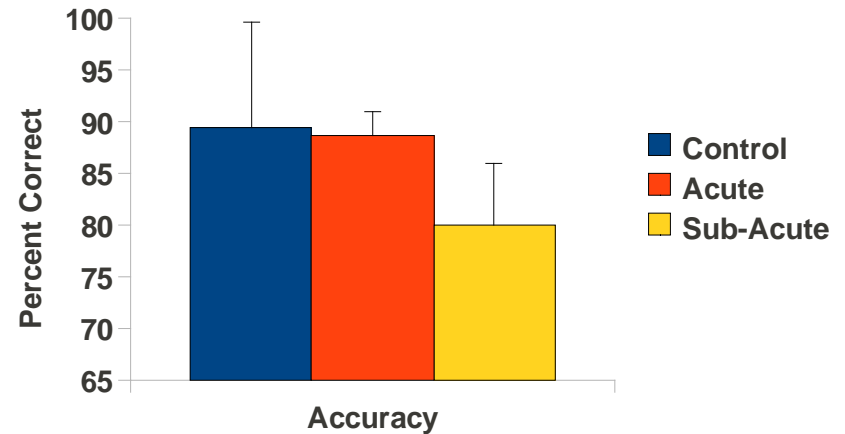
# Results from Cognitive Testing

# Results of ANAM

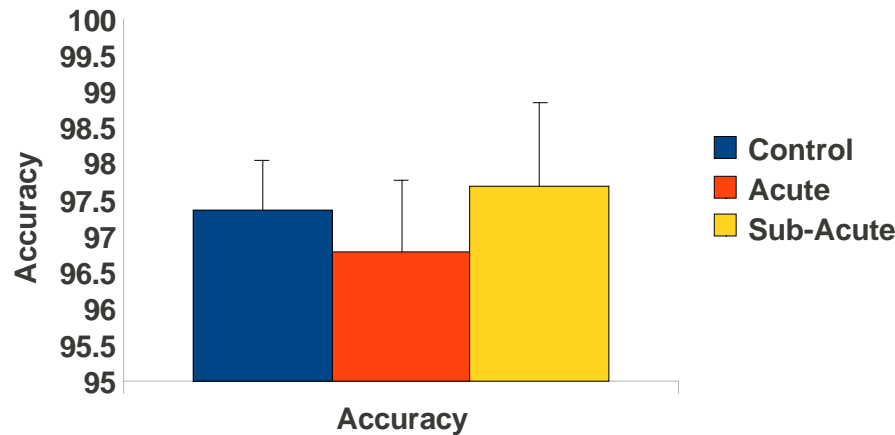
## Mathematical Processing



## Match to Sample



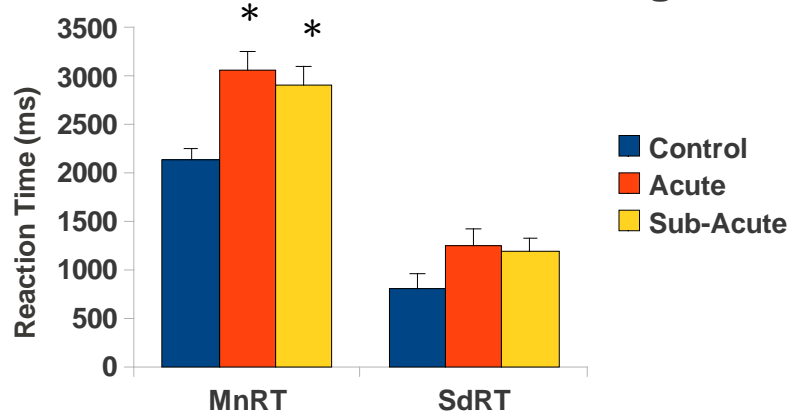
## Code Substitution



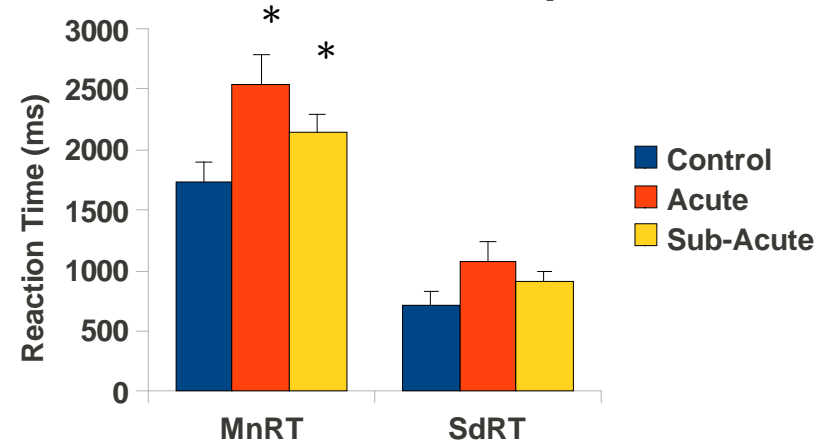
- No difference in accuracy between the controls and mTBI patients

# Results of ANAM

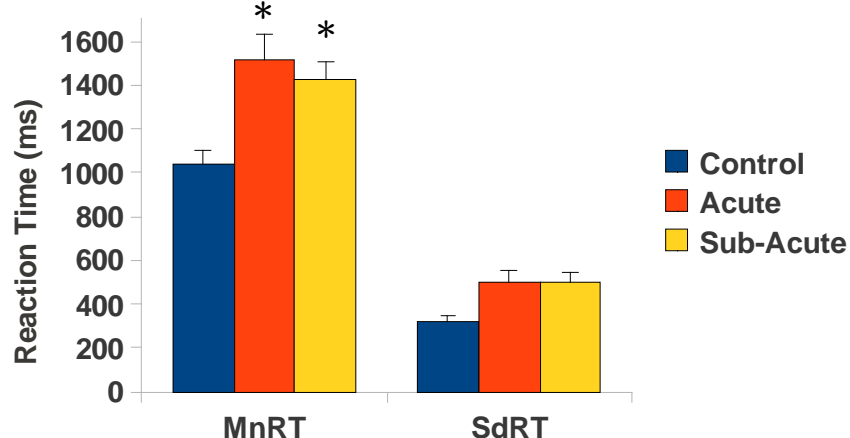
## Mathematical Processing



## Match to Sample



## Code substitution



- But mTBI patients have increased reaction times compared to controls



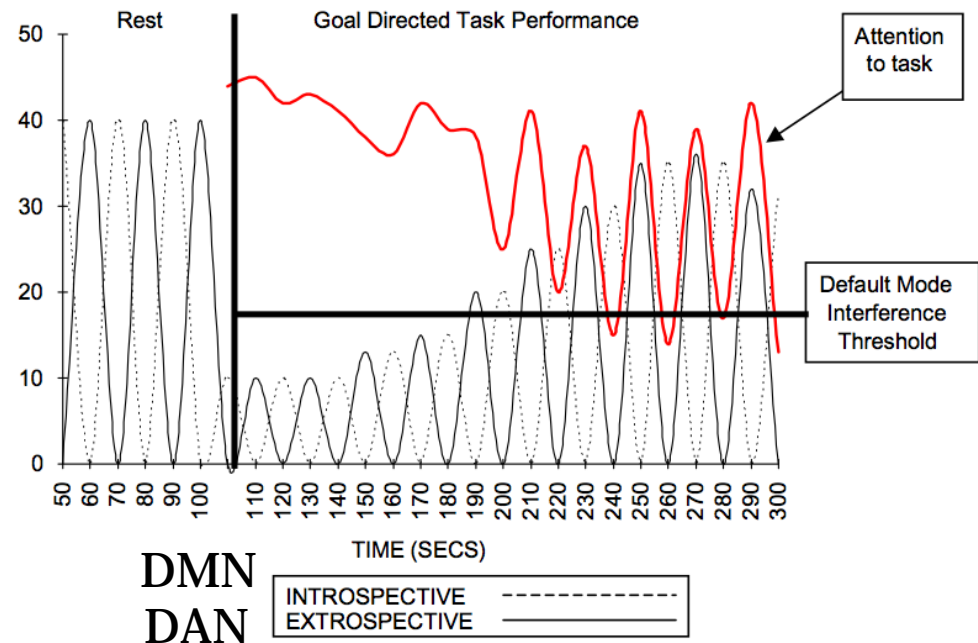
# Summary

- Following mTBI functional connectivity within the DMN is decreased during the acute and sub-acute stages
  - However, regions appear to normalize in the sub-acute stage
- Following mTBI patients are able to perform cognitive tests as accurately as controls but with an increased reaction time

# Default Mode Interference Hypothesis

- While the DMN is normally attenuated during goal directed tasks, lapses in attention are due to a failure of the DAN to suppress the activity of the DMN (Sonuga-Barke 2007)

▫ Lapses in attention cause increased reaction times





# Support from TBI Literature

- In the subacute stage (1 month) resting state functional connectivity between the DMN and DAN is increased in mTBI patients (Mayer 2011)
- mTBI patients have altered functional engagement during working memory tasks (Turner et al 2011)
- mTBI patients must allocate increased prefrontal resources to suppress the DMN during goal directed behavior.

# Future Directions

- Adding N-back working memory task to our paradigm
  - Determine activation and deactivation patterns during N-back task
  - Compare functional connectivity during N-back task to functional connectivity during rest
- Determine structure-function relationship by combining resting state MRI with Diffusion Tensor Imaging
  - Correlating these results with the individual results from the ANAM



# Acknowledgements

## Gullapalli Lab

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- ChennyZhuo
- George Makris

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- K. Shanmuganathan
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- George Wittenberg
- BizhanAarabi
- Allison Cernich
- Kevin Sheth
- Michael Makley
- Deborah Stein

DOD award # W81XWH-08-1-0725, PT 075827



# Thanks!!



# Investigation of Prognostic Ability of Novel Imaging Markers for Traumatic Brain Injury (TBI)

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Baltimore, MD 21201



# Co-PI Acknowledgements

- Dr. Kathirkamanathan Shanmuganathan - Radiologist
- Dr. Bizhan Aarabi - Neurosurgeon
- Dr. Deborah Stein – Chief, Critical Care
- Dr. Kevin Seth - Neurologist
- Dr. Michael Makley - Neurologist
- Dr. Alison Cernich – Neuropsychologist
- Members of Core Team @ Shock Trauma Center
- Jiachen Zhuo – Image Acquisition & Processing
- Steve Roys – Image Processing & Systems administrator
- Joshua Betz, Chandler Sour – Students
- Jacqueline Janowich – Coordinator

**Award Number: W81XWH-08-1-0725**

**Award Date: 15 Sep 2008**

**Award Amount: \$849,186 (total)**

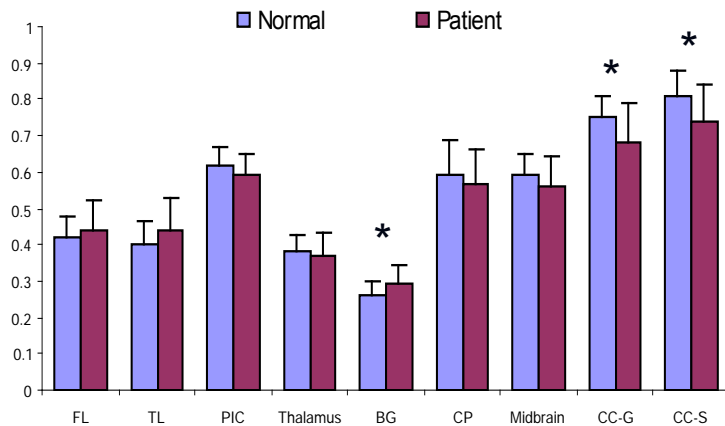
**Contract Officer Representative: Ayi Ayayi**

**Program Specialty Rep: Bao-Han Christie Vu, Ph.D.**

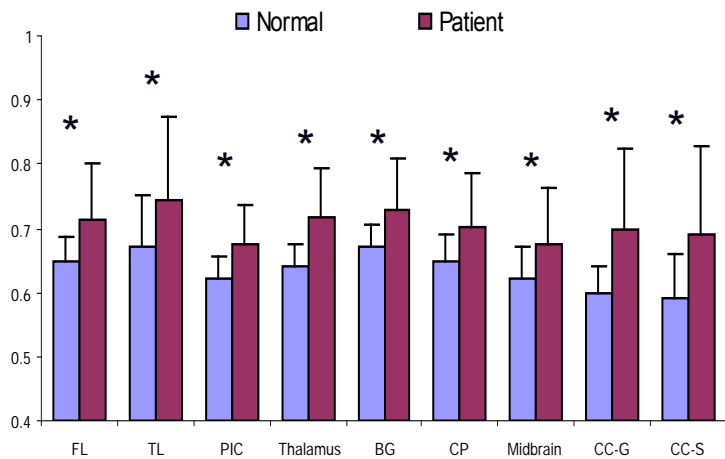
**Portfolio Manager: Kenneth C. Curley, MD**

# Study Background/Rationale

Regional FA Values



Regional ADC Values



Regional FA and ADC values for TBI patients compare to normal controls.

FL - frontal lobe

TL - temporal lobe

PIC - posterior limb internal capsule

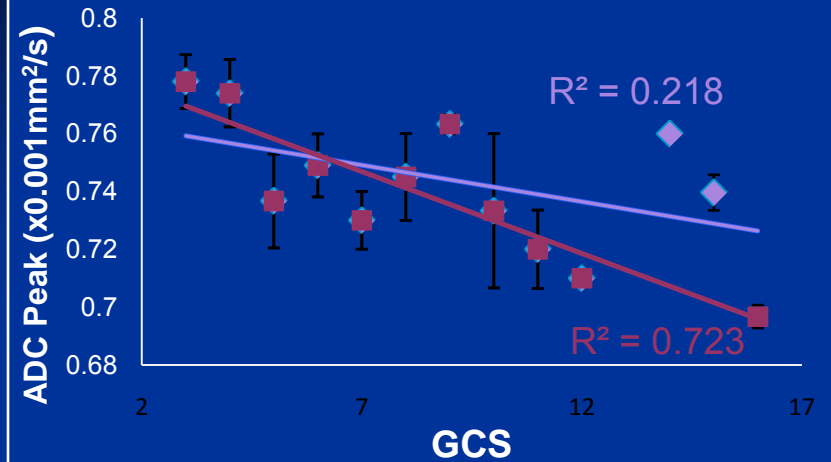
BG - basal ganglia

CP - cerebral peduncle

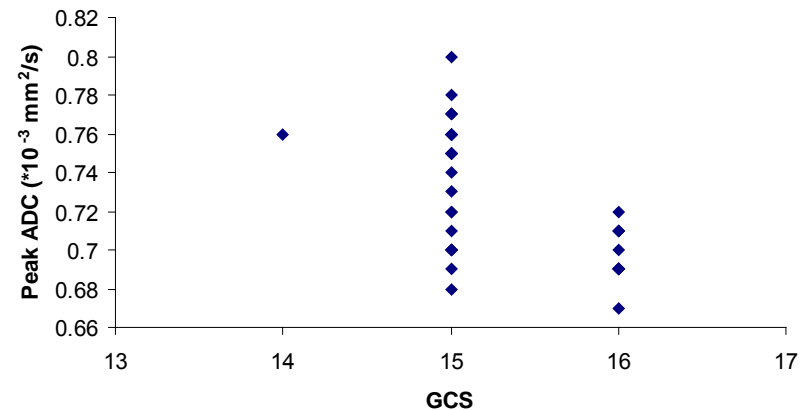
CC-G - corpus callosum - genu

CC-S - corpus callosum - splenium

ADC Peak vs. GCS



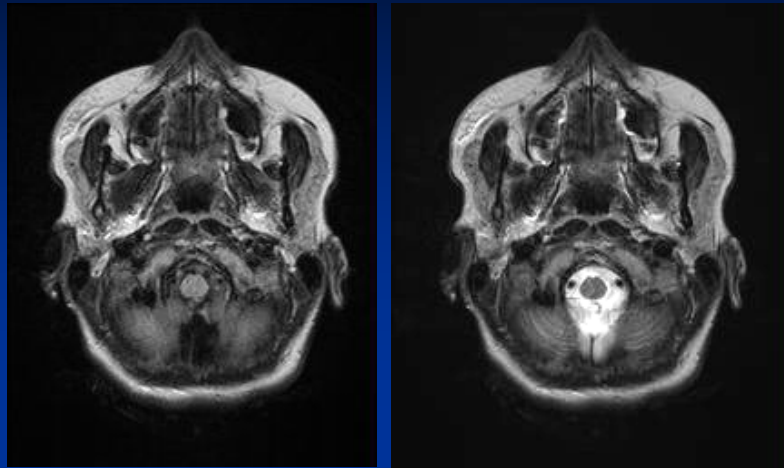
Peak ADC vs GCS



Relationship of Whole Brain peak ADC with GCS

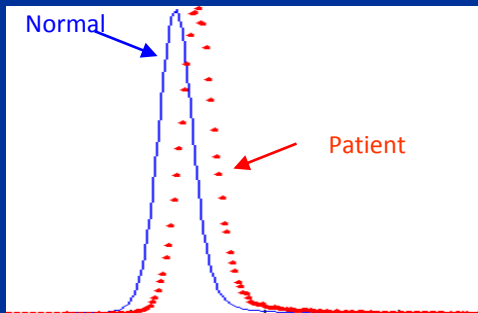


# CT and MRI Occult TBI – Value of DTI



**Normal**

**Patient**



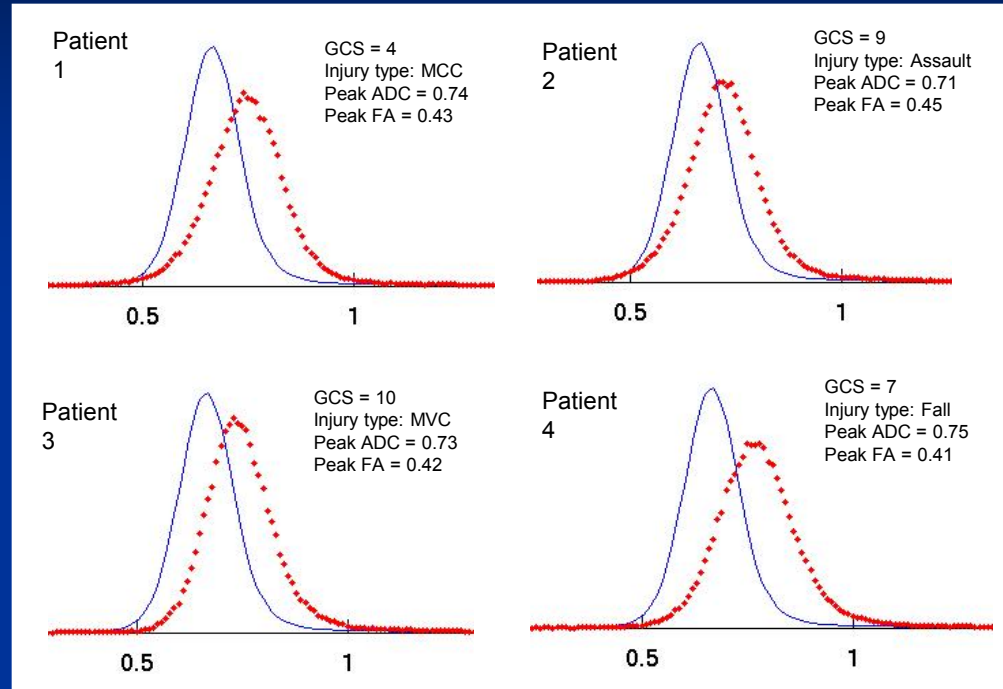
**Female, 22yr**

**GCS 15**

**Day of Injury**

**Cause: Ped struck**

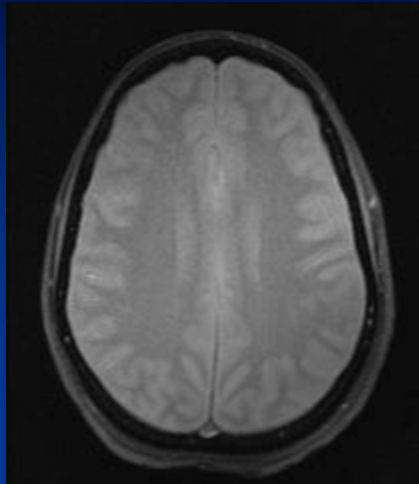
**Whole brain ADC histogram**



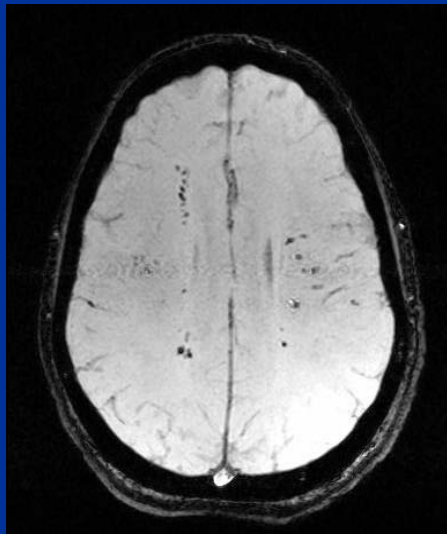
Comparison of whole brain ADC histograms on four separate patients with normal control subjects who demonstrated negative conventional MRI/CT

MCC = Motorcycle Collision, MVC = Motor Vehicle Collision.

# MRS and SWI

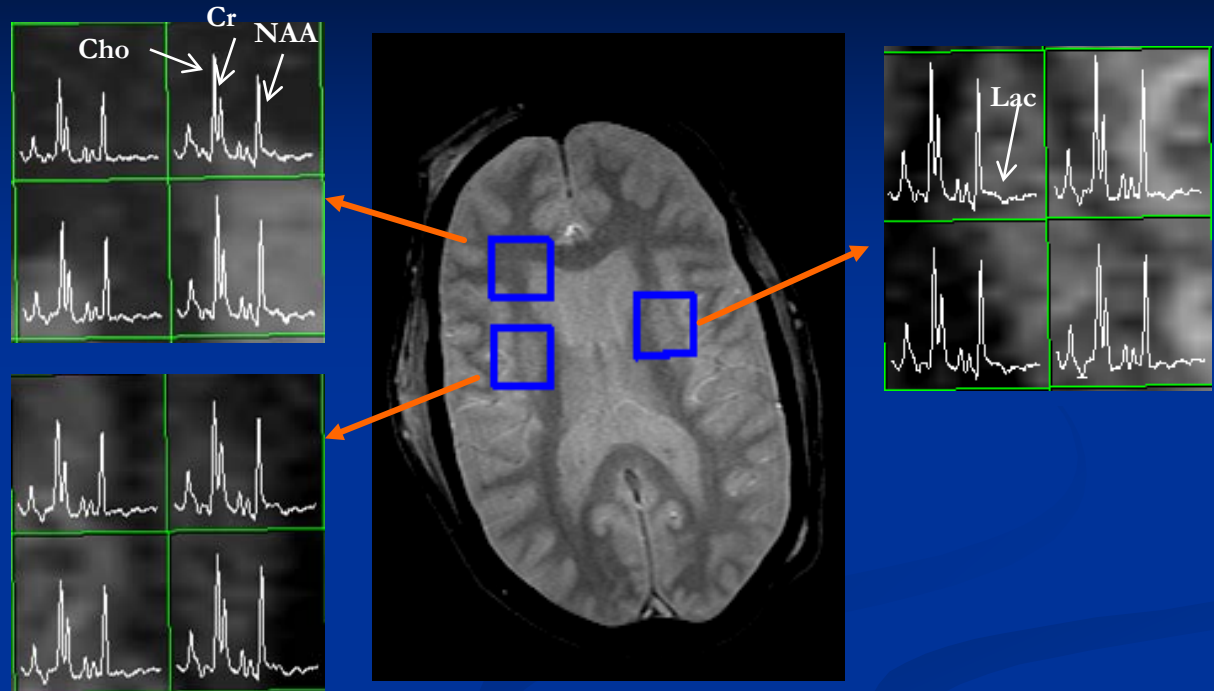


Standard T2\*-GRE



SWI

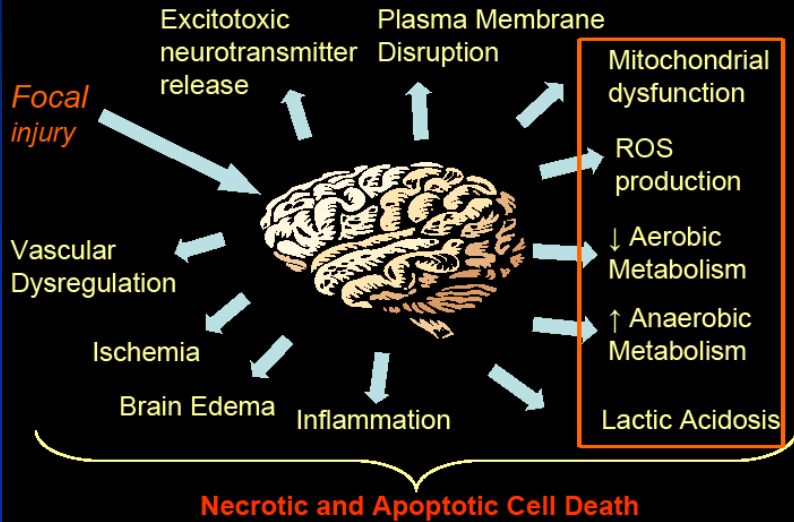
51y old male who suffered a fall with a GCS of 10. SWI demonstrates higher conspicuity and shows larger extent of injury



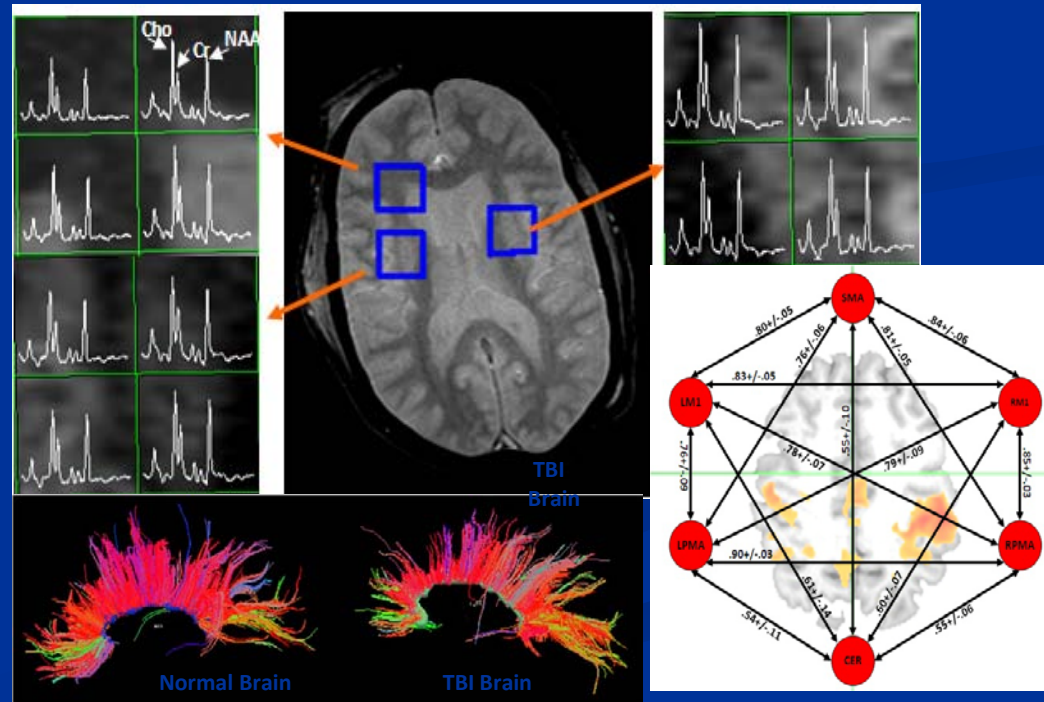
Spectra from a motor vehicle accident victim with a GCS of 5. The genu, internal & external capsule, and basal ganglia show a general decrease in NAA and an increase in the Cho/Cr ratio.

# Research Question(s)/Hypotheses

## Traumatic brain injury is complex



**Hypothesis 1:** *Patients presenting with TBI will show evidence of brain damage in the form of a biophysical, biochemical or vascular change. These changes are better detected by novel imaging techniques that will directly correlate with the clinical condition of the patient.*



Anatomic, Spectroscopic & Functional connectivity in TBI

**Hypothesis 2:** *Poor outcomes on TBI patients will correlate strongly with longitudinal changes in DTI, MRSI, and SWI markers.*

*Further, the information from a combination of these markers will demonstrate a strong correlation with the clinical status of the patient as determined by the neurocognitive test with respect to adjustment, employment, and mental health status.*

# Design and Methodology

- 120 patients; 40 each in mild, moderate and severe category
- Inclusion/Exclusion criteria
  - Age: 18+ years
  - Loss of consciousness or altered mental status
  - No history of previous TBI, psychiatric illness, white matter neurodegenerative disease, stroke, status post trauma due to asphyxiation, pregnant women
- Neuropsychological tests: ANAM battery
- Longitudinal follow up:
  - Within 5 days of injury
  - 4 weeks
  - 6 months
  - 18 months
- Normal Controls: 30 subjects, age and sex matched, two time points separated by 6 months

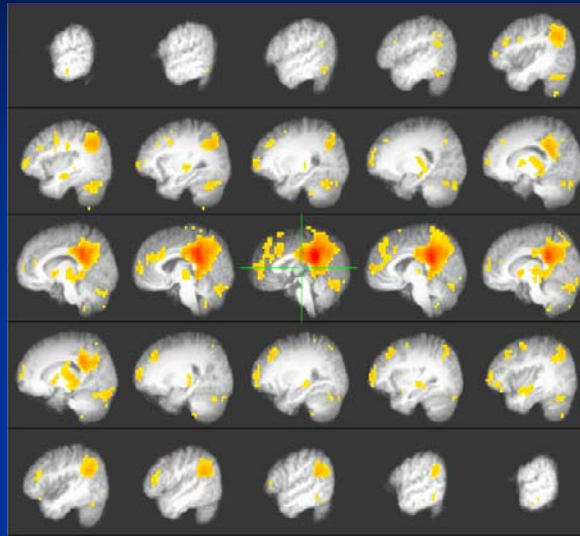
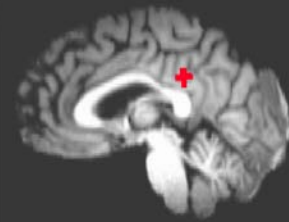
## MRI Protocol

- Localizers
- Conventional MR protocol, T2-weighted, FLAIR
- 3D-MPRAGE – for structural information & brain atrophy measurements
- DTI – 30 directional diffusion weighting at isotropic resolution with three b-values
- MR Spectroscopy – metabolic information
- Susceptibility-weighted imaging
- Arterial Spin Labeling – regional blood perfusion measurements
- Functional connectivity MRI – resting state networks

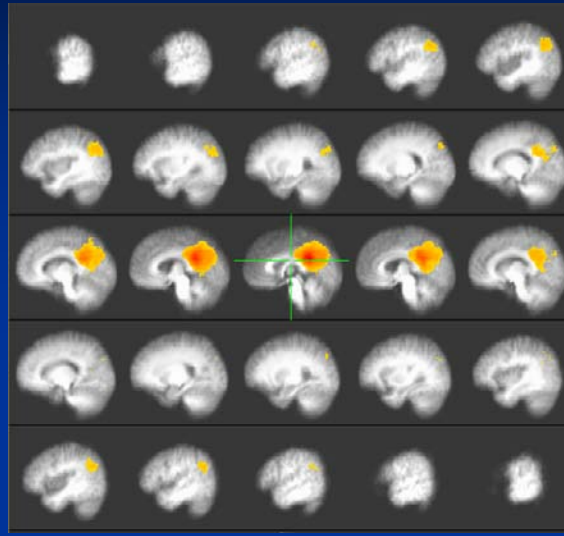


# Study Deliverable & Dissemination/Transition Plan

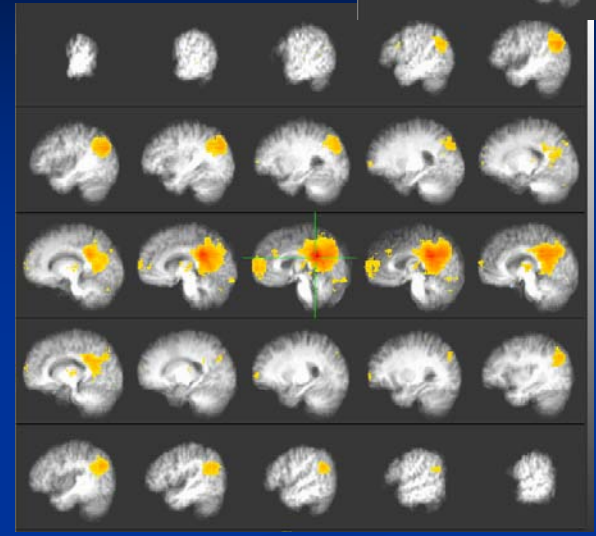
## Resting State Networks



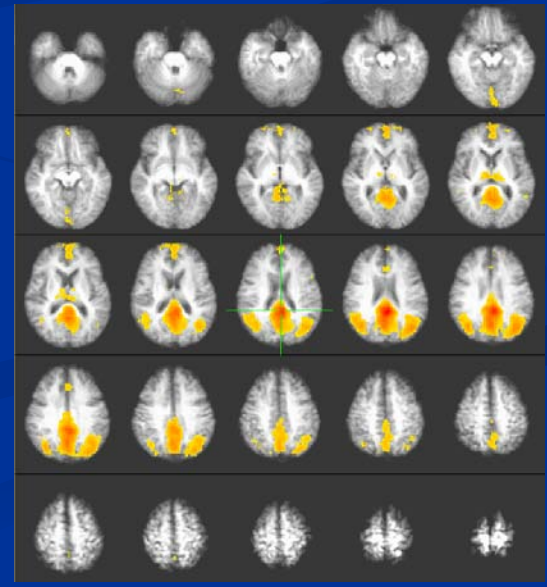
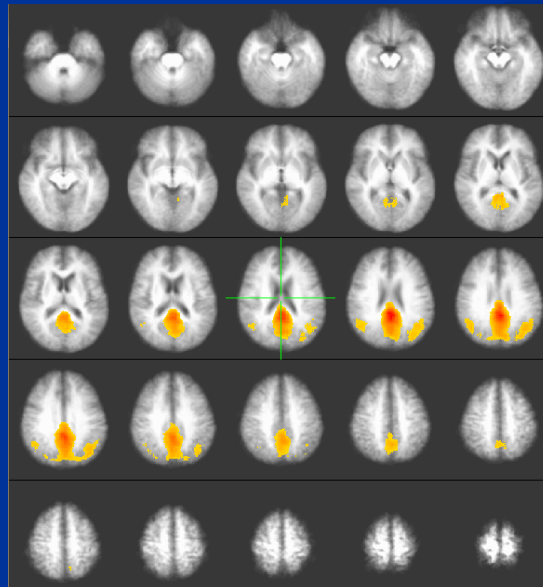
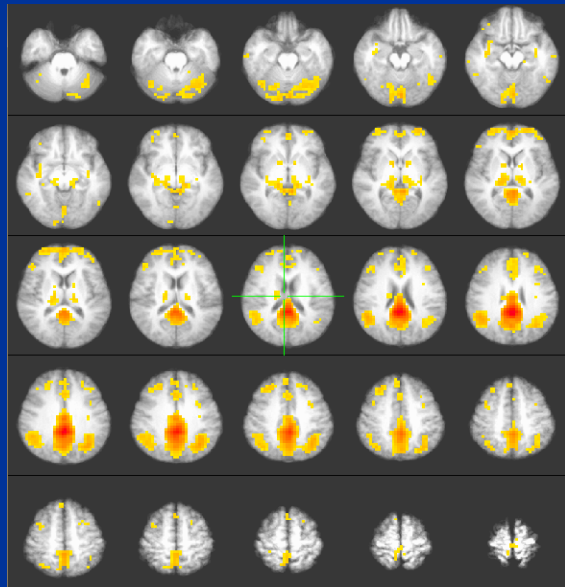
Control n=7



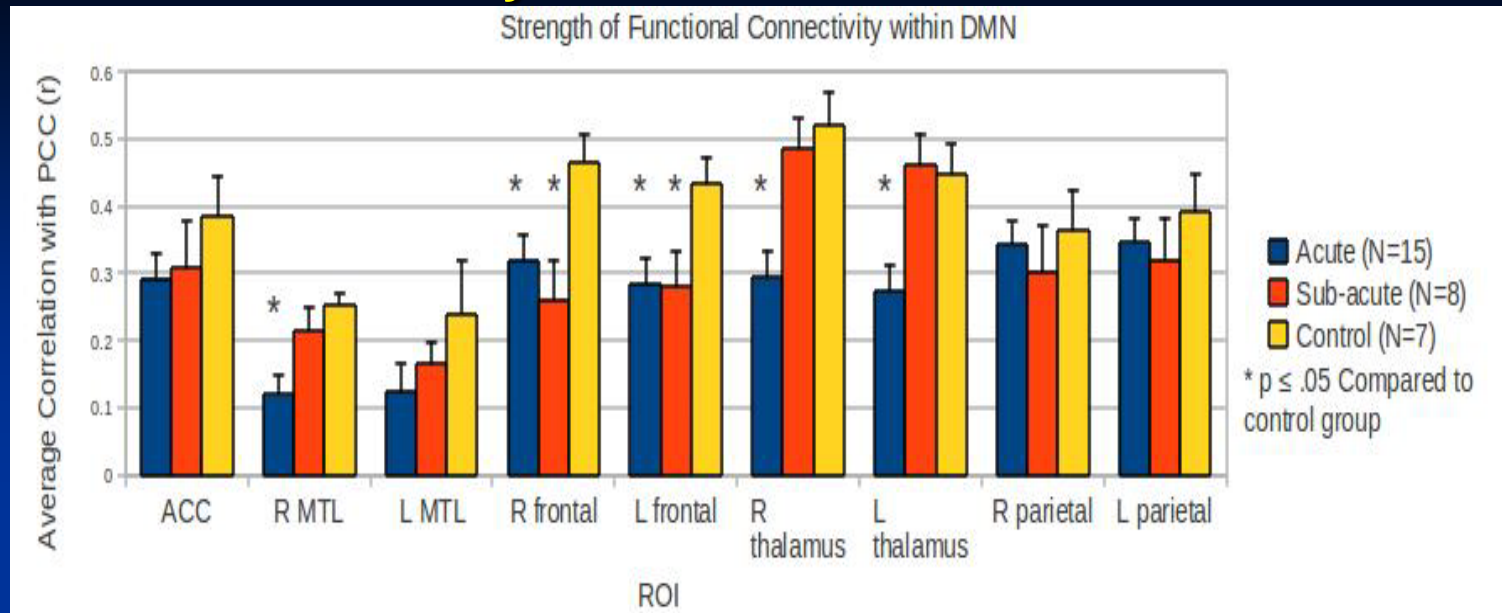
Mild TBI – Acute stage (n=15)



Mild TBI - 4 Week Visit ( n=8)

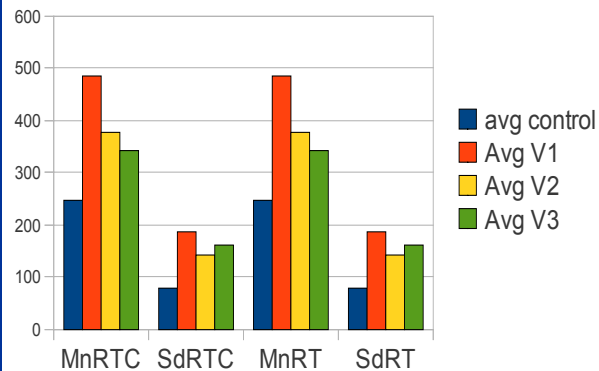


# Preliminary Results - Default Mode Network

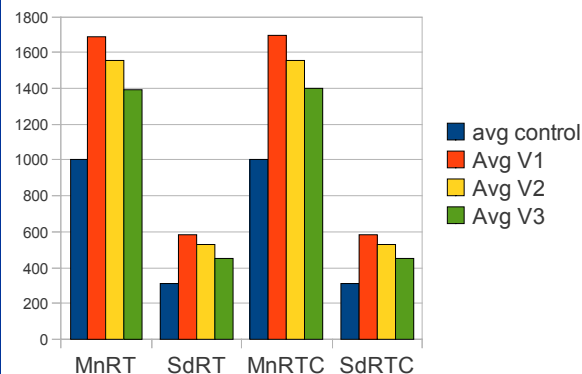


## Preliminary Results – ANAM

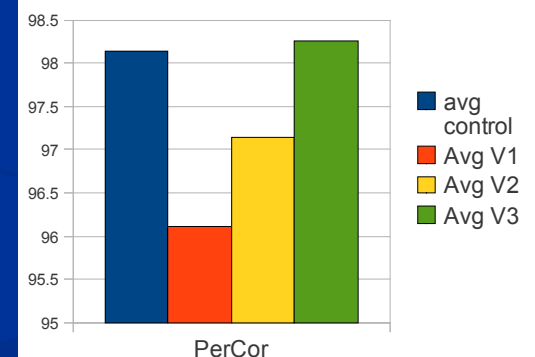
Simple Reaction Time Test



Code substitution



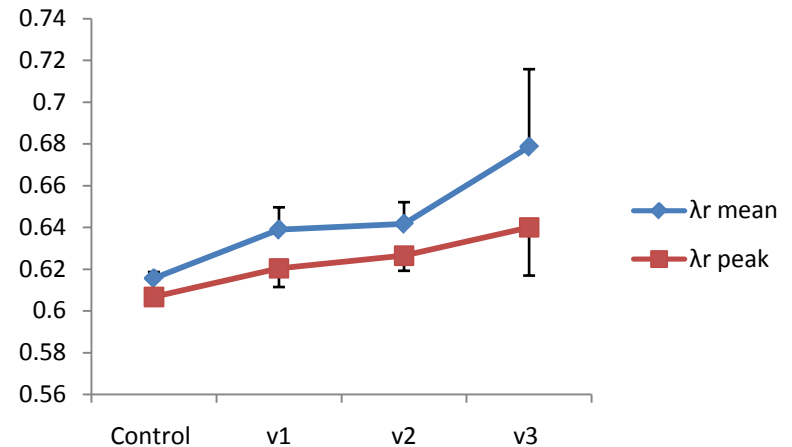
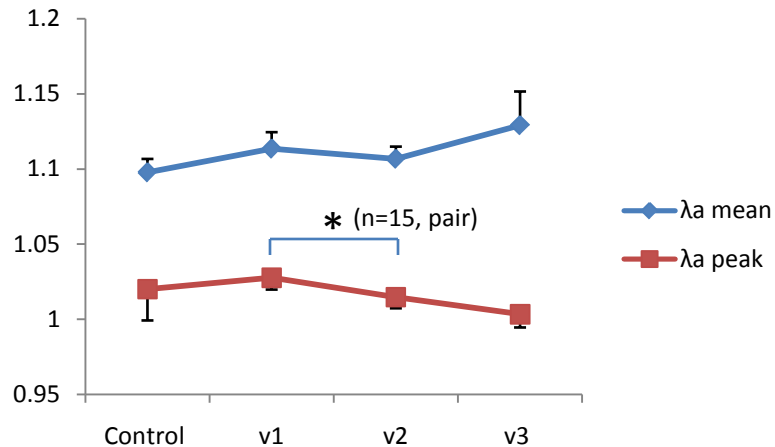
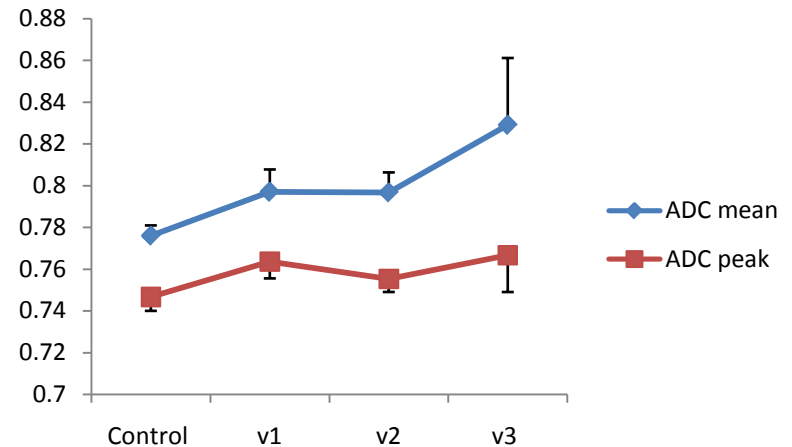
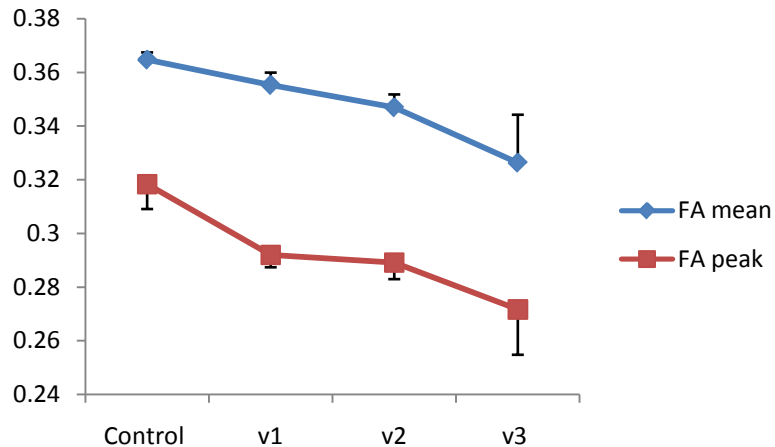
Code Substitution



- Although the number of correct answers are similar to the control subjects by visit 3, the reaction time of TBI patients continues to be significantly long.
- Similar trends were also noted in other tests (code substitution delayed, match to sample, and mathematical processing)

# Preliminary Results – DTI

## Whole Brain White Matter Values



Control (n = 3), v1 (n = 26), v2 (n = 17), v3 (n = 3).

# Diffusion Kurtosis – the Non-Gaussian property of water diffusion

Diffusion Equation:  $\ln \frac{S(b)}{S(0)} = -bD$

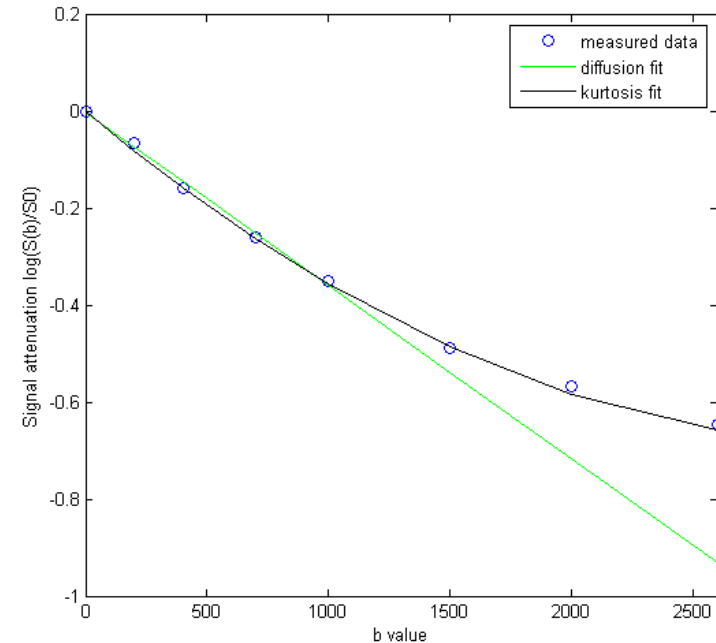
Excess kurtosis is defined as:

$$K = \frac{\mu_4}{\mu_2^2} - 3$$

Where  $\mu_i$  is the i-th central moment of the distribution.

Kurtosis Model:

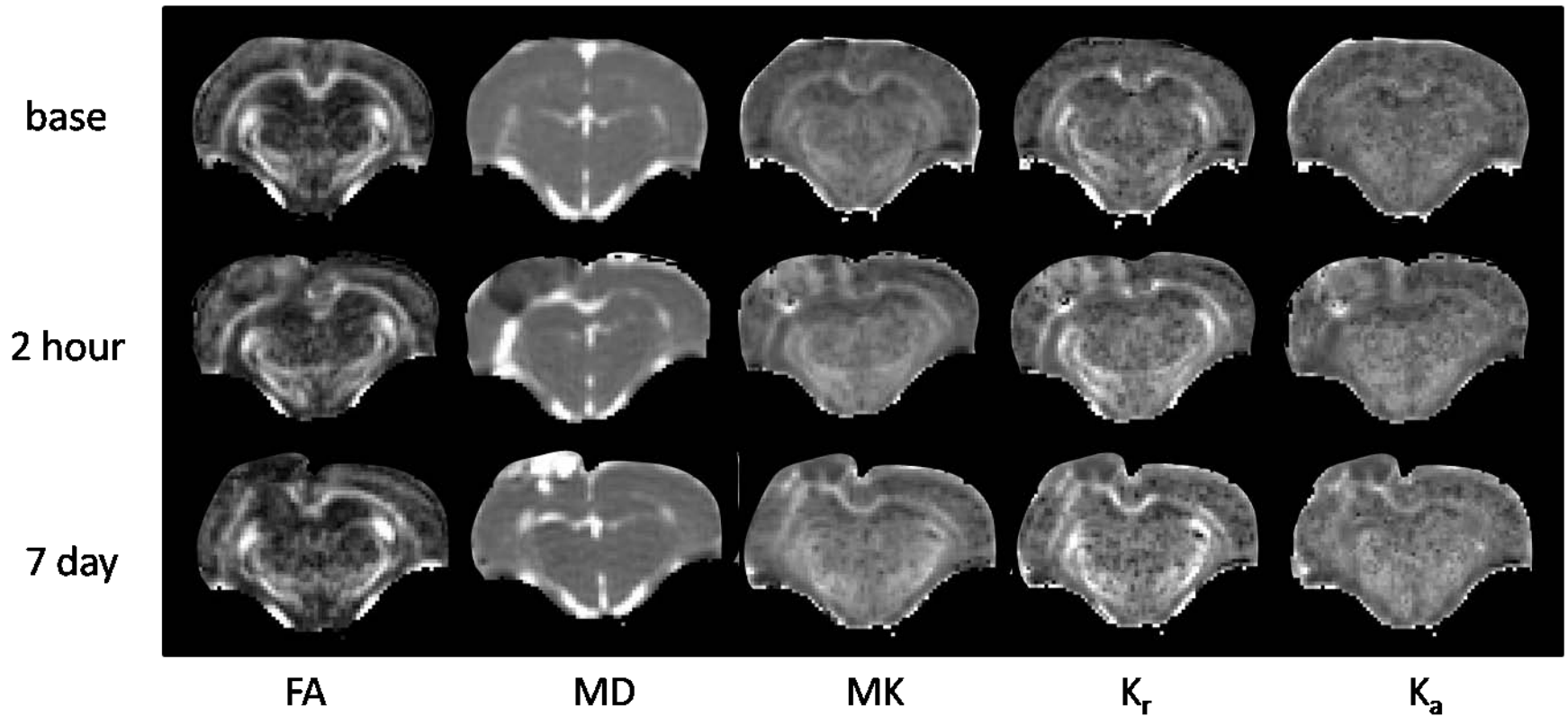
$$\ln \frac{S(b)}{S(0)} = -bD_{app} + \frac{1}{6}b^2D_{app}^2K_{app} + O(b^3)$$



So by measuring DW signals with multiple b-values, we can estimate  $D_{app}$  and  $K_{app}$  along a specific diffusion direction by fitting above equation.



# Diffusion Kurtosis

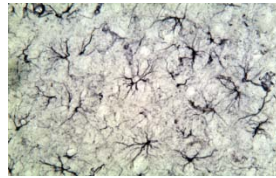


# Diffusion Kurtosis – Imaging Marker for Astrogliosis?

## a Astrocytes in healthy CNS tissue



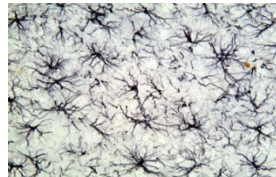
- Not all astrocytes express detectable levels of GFAP
- Astrocytes have non-overlapping domains
- Little or no proliferation



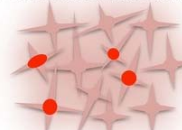
## b Mild to moderate reactive astrogliosis



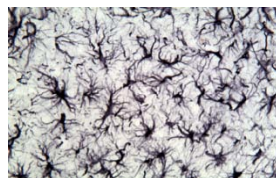
- Most astrocytes are GFAP+
- Preservation of individual domains
- Little or no proliferation



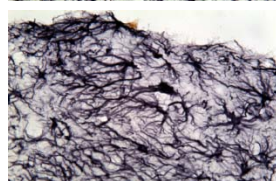
## c Severe diffuse reactive astrogliosis



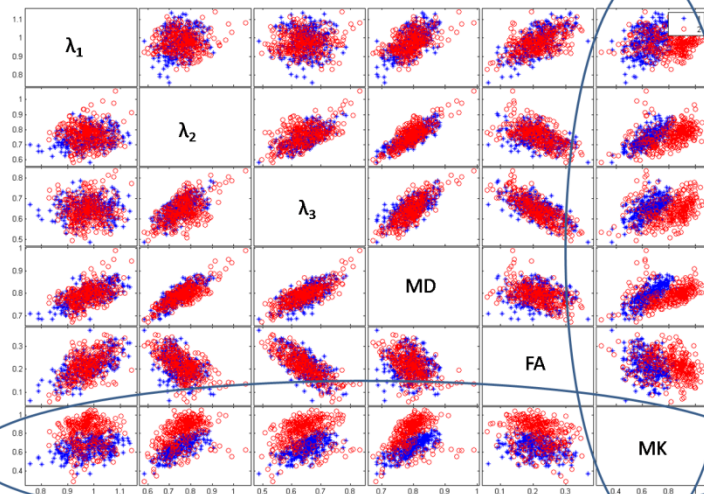
- Most astrocytes are GFAP+
- Disruption of individual domains
- Proliferation



## d Severe astrogliosis with compact glial scar formation

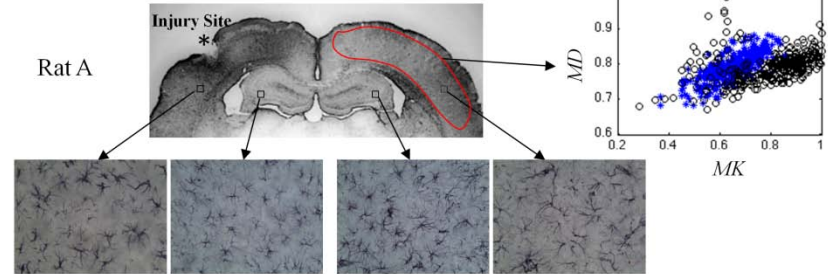


Sofroniew & Vinters, Acta Neuropathol 2010

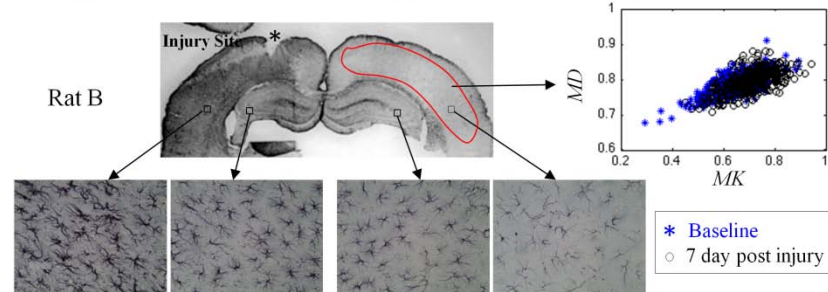


Blue: base Red: 7 day post injury

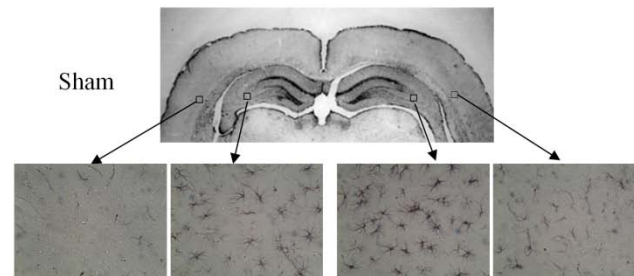
Rat A



Rat B



Sham



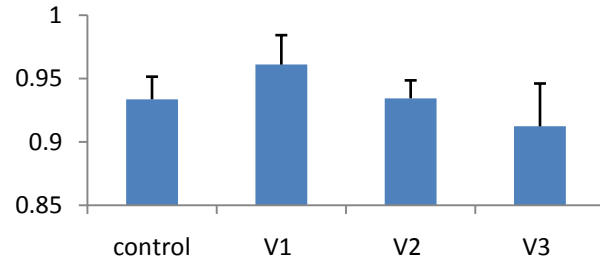
Glial fibrillary acidic protein (GFAP) Immunohistochemical staining

- Changes in mean kurtosis is associated with increased GFAP immunoreactivity
- These changes are not easily detected by normal diffusion tensor imaging parameters.
- Mean Kurtosis appears to be a sensitive marker in gray matter regions

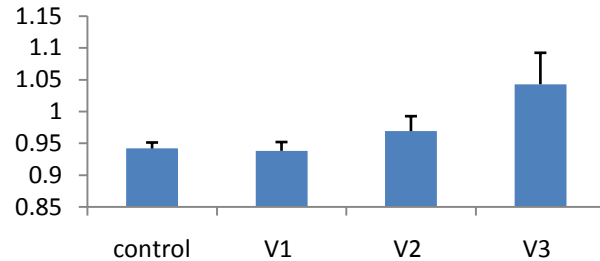
# Whole brain values from segmented white/grey matter regions

## White matter

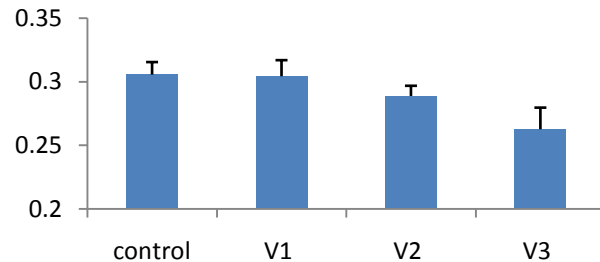
### MK mean



### ADC mean

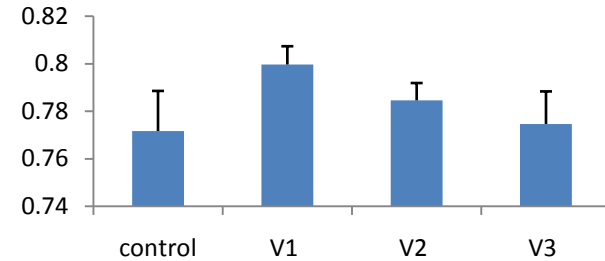


### FA mean

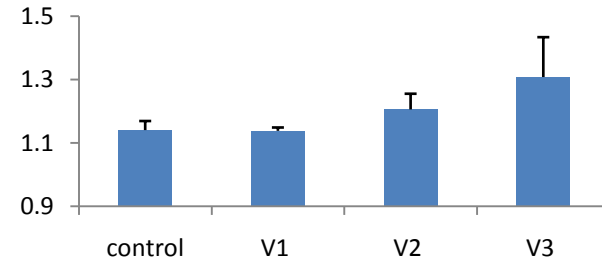


## Grey matter

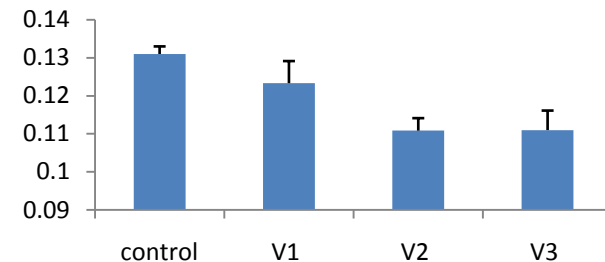
### MK mean



### ADC mean



### FA mean



Control (n = 3), v1 (n = 3), v2 (n = 7), v3 (n = 3).

# Study Progress

TOTAL PATIENTS CONSENTED TO DATE: 70

TOTAL PATIENTS ACTUALLY ENROLLED IN STUDY: 32

## Patients actually enrolled in study

	<i>Initial</i>	<i>1 month</i>	<i>6 month</i>
<i>Mild</i>	24	15	3
<i>Moderate</i>	3	2	1
<i>Severe</i>	5	2	1
<i>Total TBI</i>	32	19	5
<i>Healthy Controls</i>	3	NA	0

## ■ Publications/Presentations

- ISMRM & OHBM abstract on Resting State Networks
- Conducting Symposium at the Federal Interagency Conference on TBI in Washington with Dr. Theresa Pape (June 2011)
- Manuscript for the Journal 'BRAIN' on Application of Diffusion Kurtosis in TBI.

## ■ Barriers and Contingencies

- Recruitment of moderate/severe injury patients. Working with NIH to boost recruitment (Dr. Larry Latour).

## ■ Expenditures

- In control until the official end of the grant – 9/15/2011.
- Will have issues in terms of retaining support personnel critical for recruitment and data analysis.
- Patient related expenses should be fine under no cost extension.

## ■ Next Steps

- Continue efforts with patient recruitment, data analysis and manuscript generation. Increase enrolled to consented ratio. Reasonably confident that we will meet recruitment goals if no-cost approval is obtained
- Pursue the effectiveness of diffusion kurtosis as an imaging marker of injury
- Compare and contrast imaging findings from civilian TBI with military related injuries – Dr. Gerard Riedy

# Study Progress

## ■ Current and Anticipated Challenges

- Recruitment of moderate and severe injury patients – nursing and transportation issues.
- Budget related challenges. Retain key personnel for recruitment and data analysis.
- Coordination of activities between the NIH group and ours – mainly IRB and patient logistics.
- Comparison of civilian data with military related data

## ■ Efforts to Address Challenges

- Pressure from various investigators to hire a full time research nurse for monitoring sedated patients especially during imaging studies.
- Working with program coordinator and others to ensure continued support of essential personnel. Looking for additional grant funding.
- Pursuing active partnership with Dr. Gerard Riedy to compare data between civilian and military injuries. Also pursuing additional funding for data analysis.



# MRI Metrics in the Horizon

**Rao P Gullapalli**

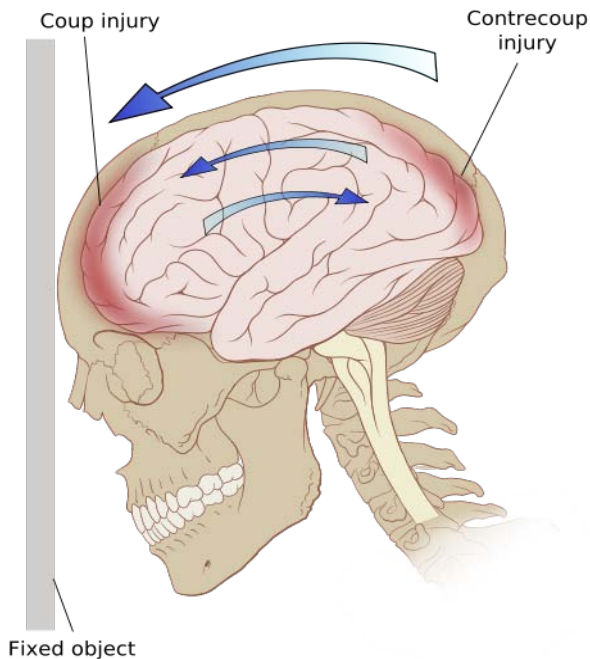
Department of Diagnostic Radiology &  
Nuclear Medicine

University of Maryland School of Medicine  
Baltimore, MD 21201



# Traumatic Brain Injury

Traumatic injuries remain the leading cause of death in children and in adults aged 45 years or younger.



## **Primary injury:**

Structural changes due to mechanical forces

## **Secondary injury:**

Widespread degeneration of neurons, glial cells, axons

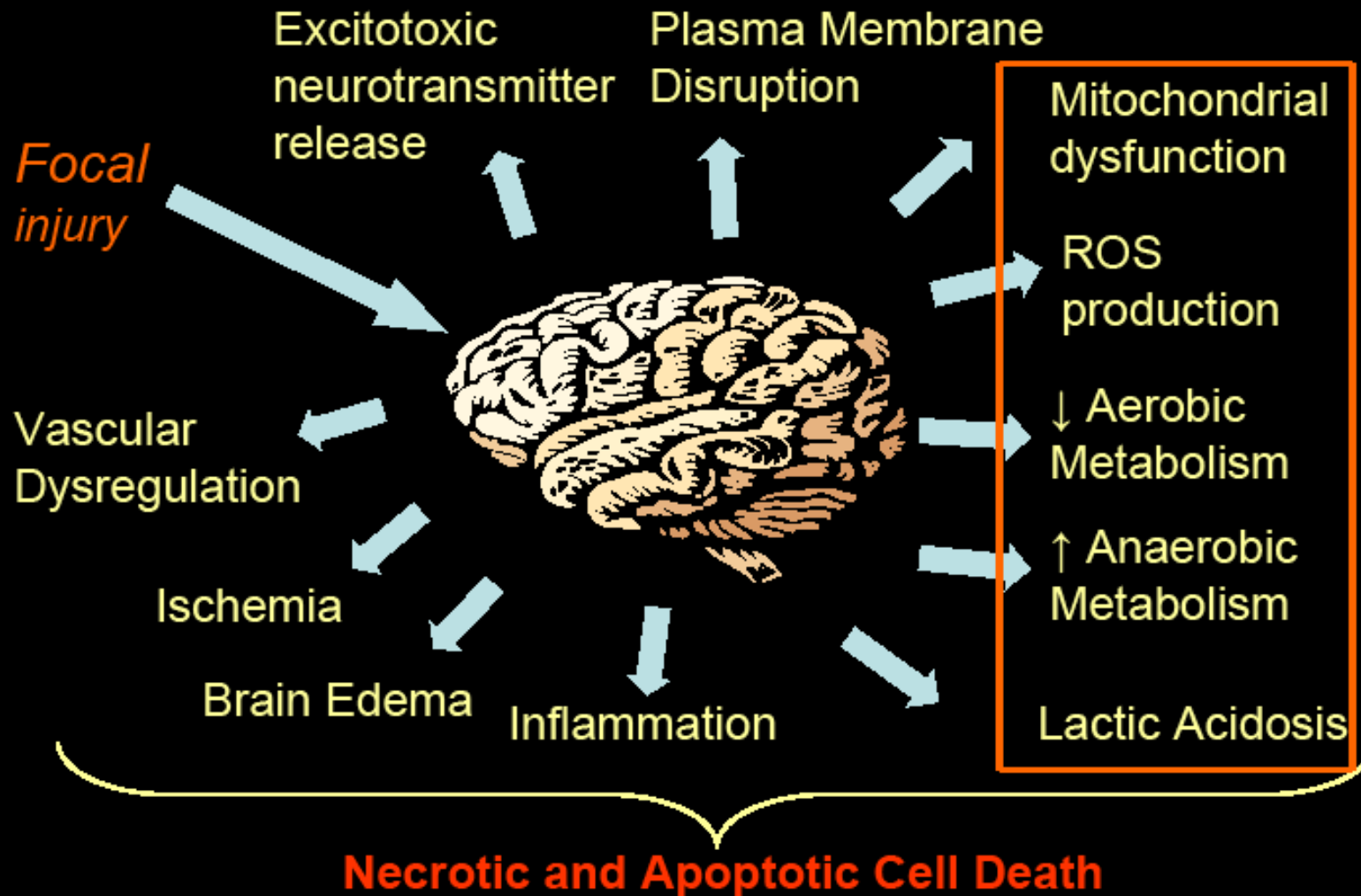
**Patient outcome is hard to predict!**

The major focus of TBI management:

**Prevention of secondary injuries**

# The Problem!

## Traumatic brain injury is complex



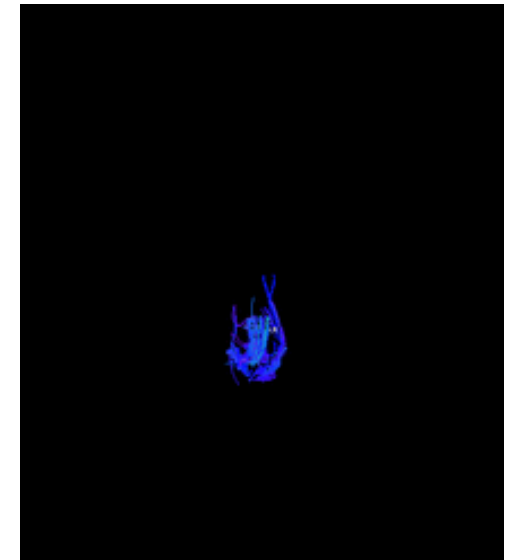
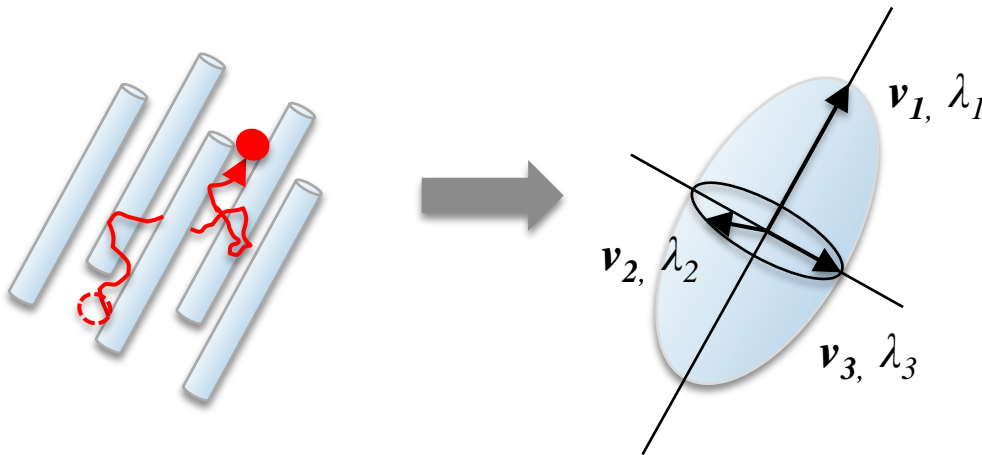


# Advanced MRI Techniques

- Diffusion Tensor Imaging – Kurtosis
- Arterial Spin Labeling
- Whole Brain Spectroscopy
- Susceptibility-weighted imaging
- Resting state MRI

# Diffusion Tensor Imaging

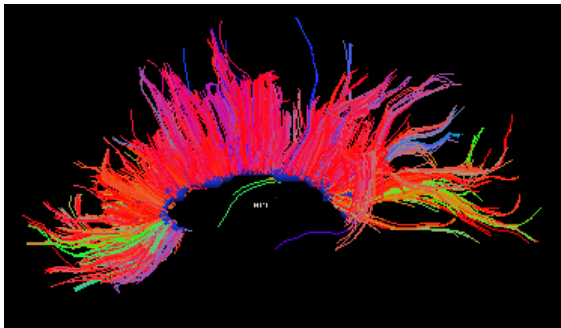
- Understanding tissue alterations at an early stage following traumatic brain injury (TBI) is critical for injury management and prevention of more severe secondary damage to the brain.
- Diffusion tensor imaging (DTI) is a powerful tool for studying white matter microstructure change.



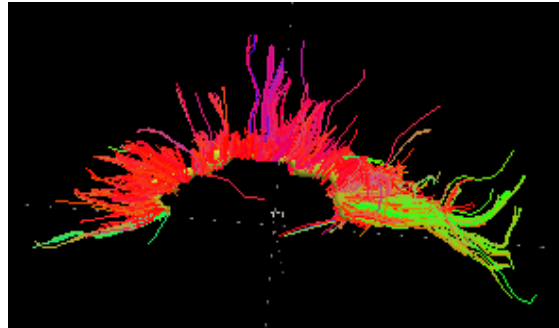
- DTI has been used extensively in evaluating axonal damage following TBI.

# Diffusion Tensor Imaging in Evaluating TBI

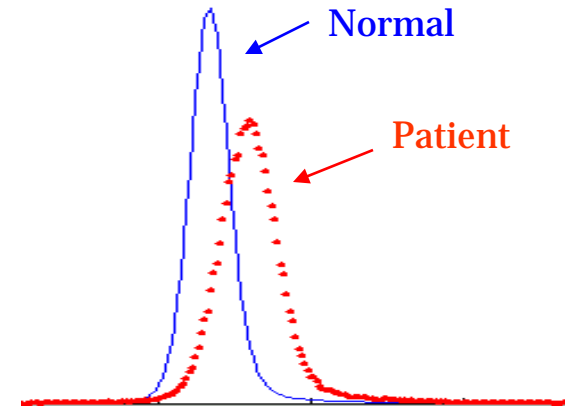
Normal



Patient

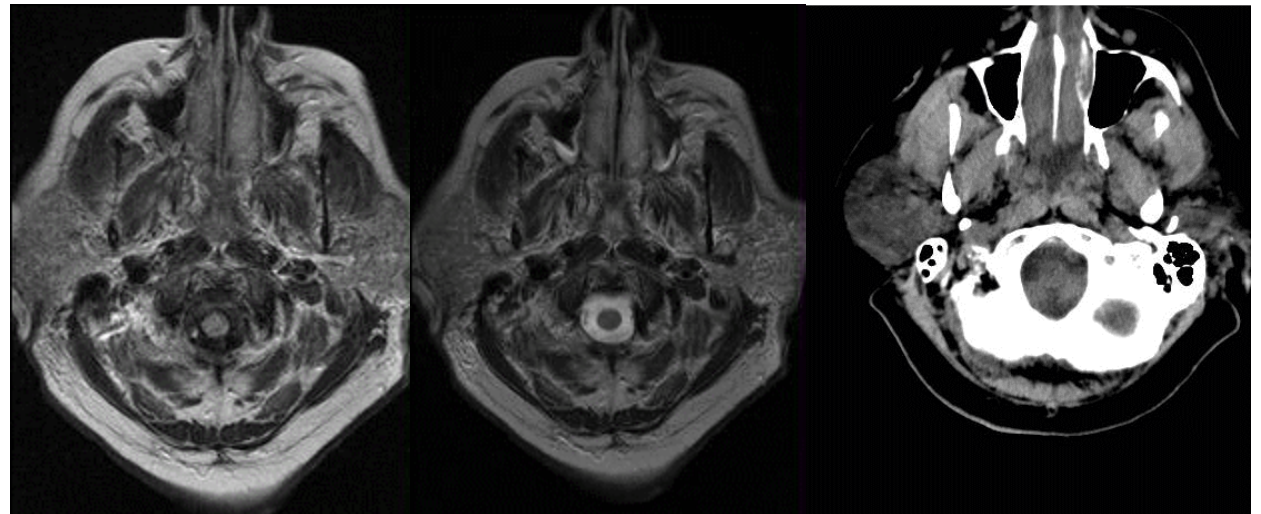


Whole brain ADC histogram



**Abnormal DTI**  
despite negative  
conventional MRI  
and CT findings!

GCS 5, MVC, 38y M



# Does normal DTI mean no injury?

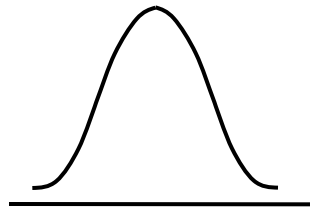
- Acutely post injury:
  - Increased *FA*
  - Reduced *MD*
  - Possible cause: cytotoxic edema, reduced extracellular space, etc.
- Chronic stage:
  - Reduced *FA*
  - Increased *MD*
  - Possible cause: edema, cellular destruction, axonal degeneration, etc.
- At sub-acute stage, DTI parameters may undergo pseudo-normalization<sup>1,2</sup>.
- Does this mean there is no injury?

# Beyond DTI: Diffusion Kurtosis

— the Non-Gaussian property of water diffusion



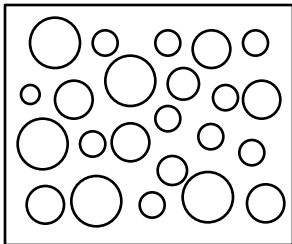
Uniform water diffusion



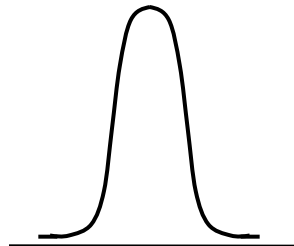
$K=0$

Gaussian  
(**DTI**)

$$\ln \frac{S(b)}{S(0)} = -bD$$



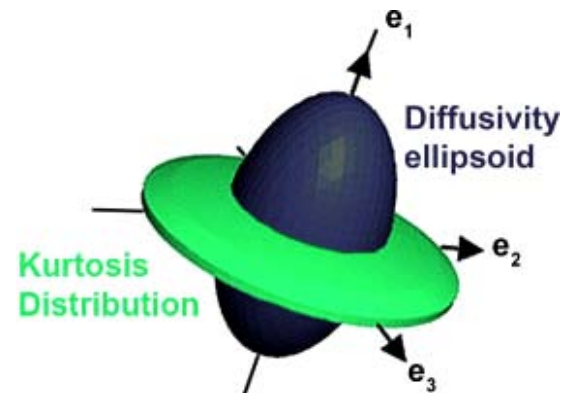
Non-uniform water diffusion



$K>0$

Non-Gaussian  
(**DKI\***)

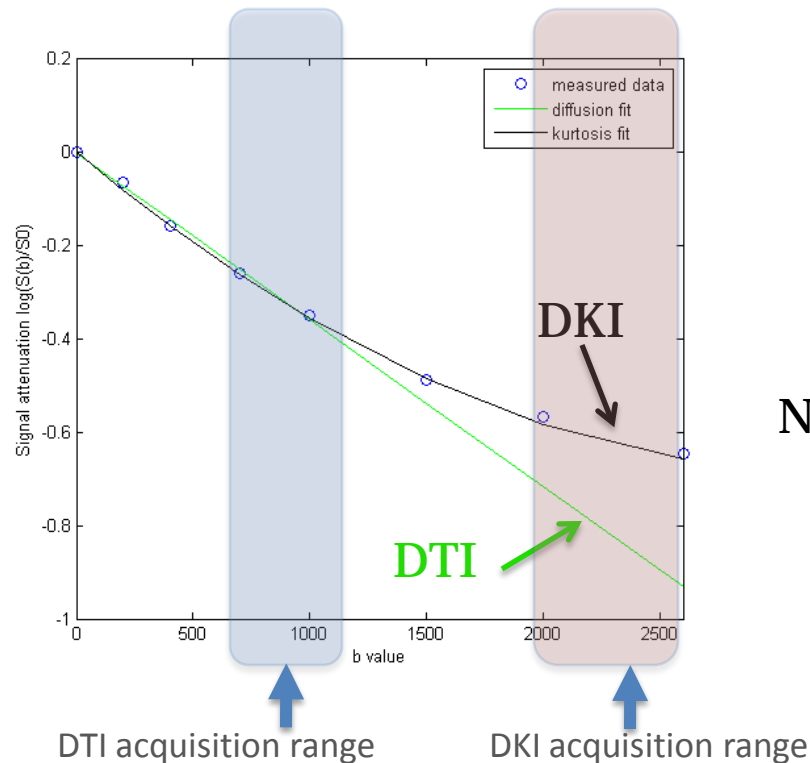
$$\ln \frac{S(b)}{S(0)} = -bD + \frac{1}{6}b^2D^2K$$



\* Jensen JH, et al. Magn Reson Med. 2005; 53:1432-40.

# Diffusion Kurtosis

— the Non-Gaussian property of water diffusion



Gaussian  
(**DTI**)

$$\ln \frac{S(b)}{S(0)} = -bD$$

Non-Gaussian  
(**DKI\***)

$$\ln \frac{S(b)}{S(0)} = -bD + \frac{1}{6}b^2D^2K$$

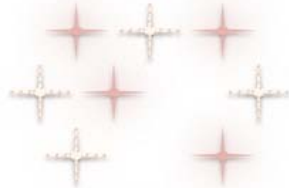
## Diffusion kurtosis

- tissue complexity (heterogeneity)<sup>1</sup>
- higher sensitivity in characterizing tissue microstructure<sup>2,3</sup>

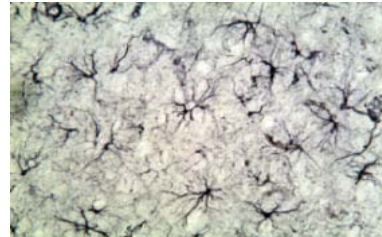
<sup>1</sup> Jensen JH, Helpern JA, 2010. <sup>2</sup> Falangola MF et al, 2008. <sup>3</sup>Hui ES et al., 2008.

# Tissue microstructure & kurtosis

## a Astrocytes in healthy CNS tissue



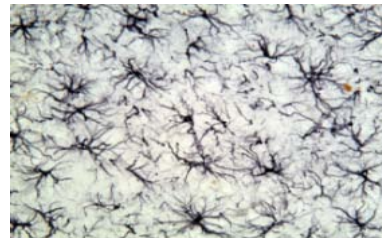
- Not all astrocytes express detectable levels of GFAP
- Astrocytes have non-overlapping domains
- Little or no proliferation



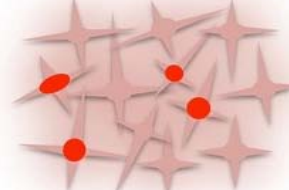
## b Mild to moderate reactive astrogliosis



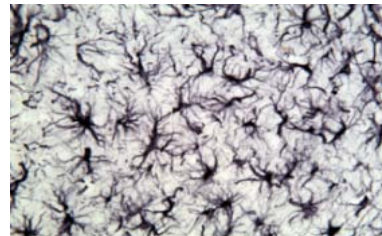
- Most astrocytes are GFAP+
- Preservation of individual domains
- Little or no proliferation



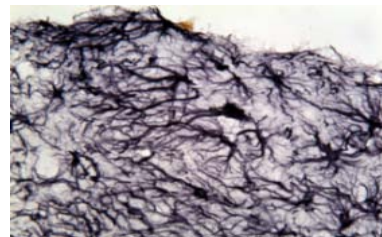
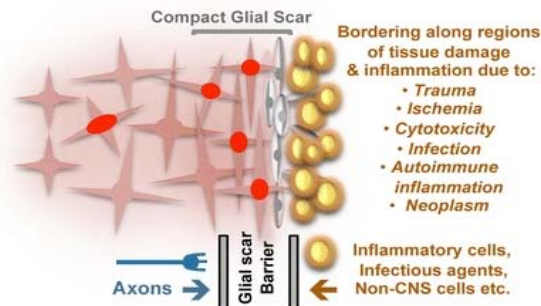
## c Severe diffuse reactive astrogliosis



- Most astrocytes are GFAP+
- Disruption of individual domains
- Proliferation



## d Severe astrogliosis with compact glial scar formation



Increased severity of injury

MK ↑

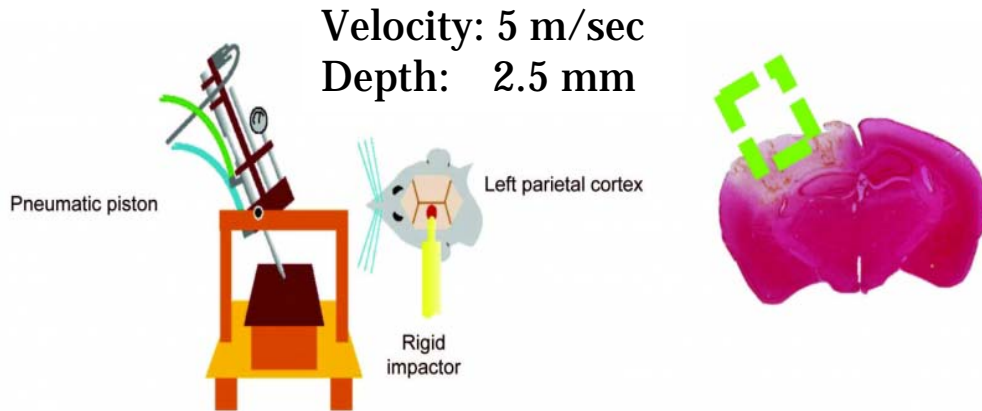
# Diffusion Kurtosis

- Can diffusion kurtosis parameters provide information over and beyond that available from DTI parameters regarding tissue damage following TBI
- If so, is DKI also sensitive to microstructure changes in grey matter



# Animal Preparation

## Controlled Cortical Impact (CCI) injury model\*



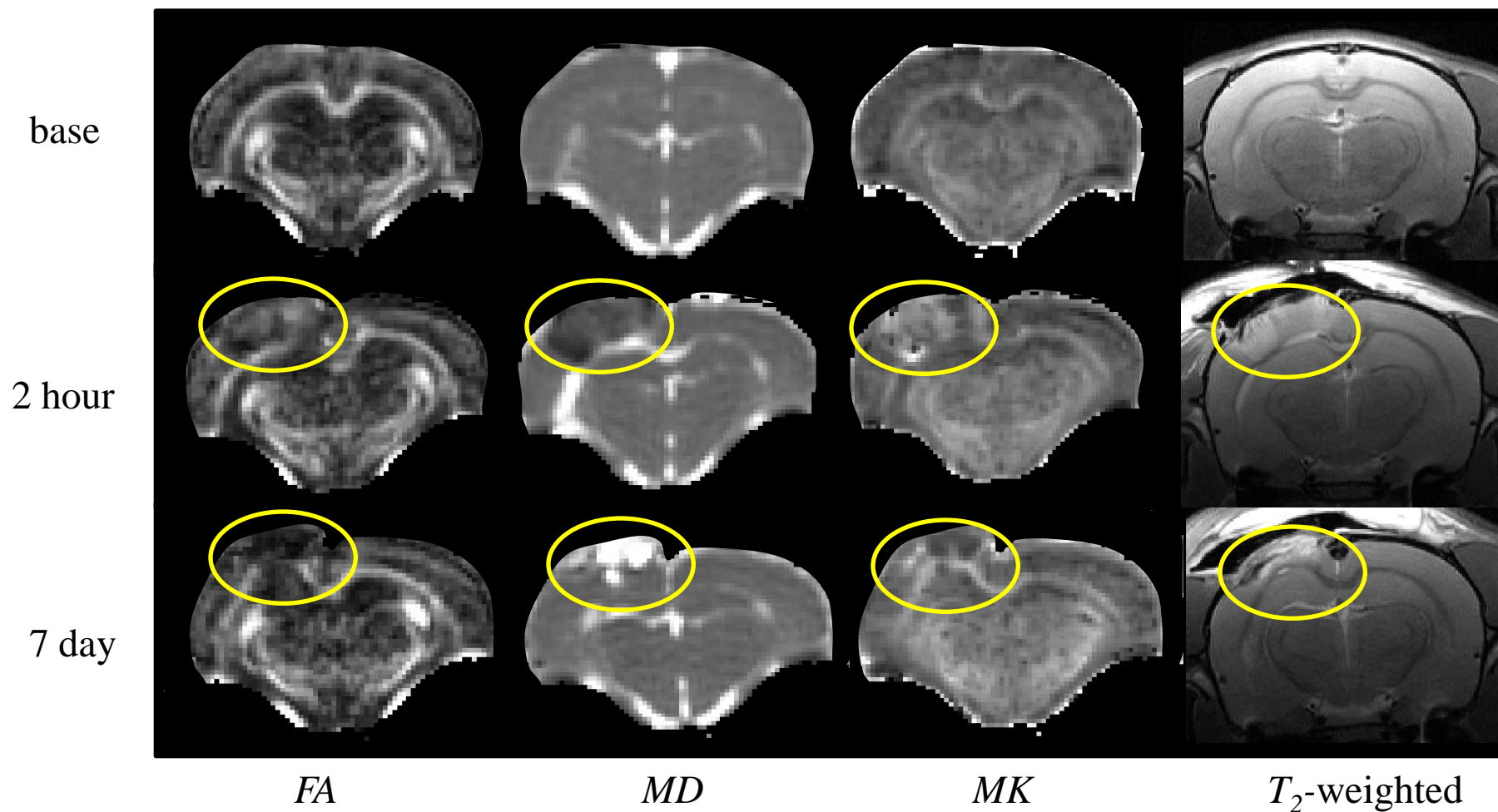
### **DKI protocol:**

- 30 directions
- 2 b-values  
( $b=1000$  and  $2000 \text{ s/mm}^2$ )
- 2 averages
- $TR/TE = 6000/50 \text{ ms}$

- Rats (Adult male Sprague-Dawley):  $n = 12$
- Imaging (Bruker 7T): baseline (1 day before injury)  
acute stage (2 hours post injury)  
sub-acute stage (7 days post injury,  $n = 7$ )
- Histology: 7 days post injury after imaging

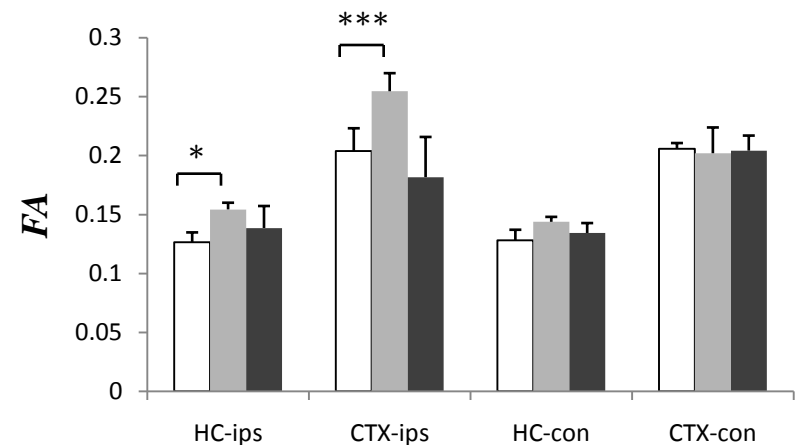
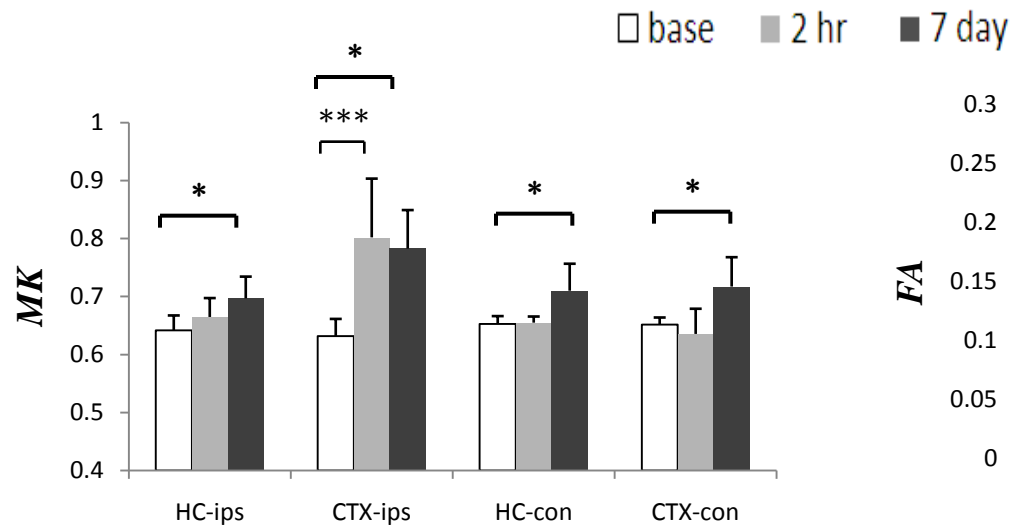
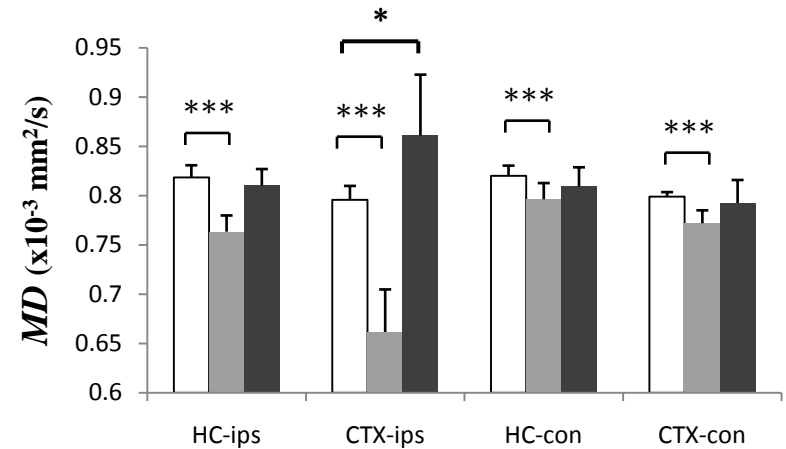
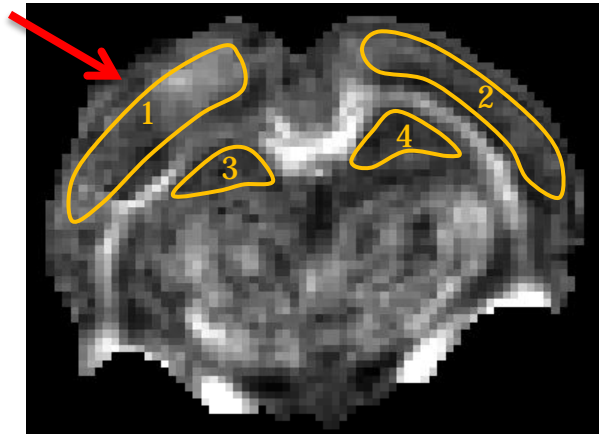
\* Dixon et al., J Neurosci Methods. 1991; 39:253-62.

# Parametric maps of a representative rat



# Regional evolution of DKI parameters

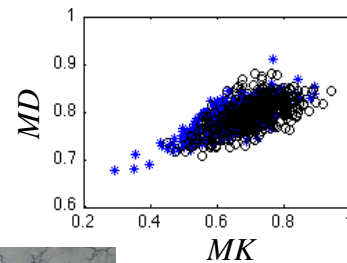
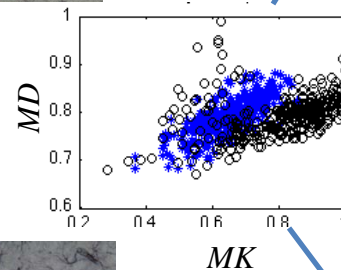
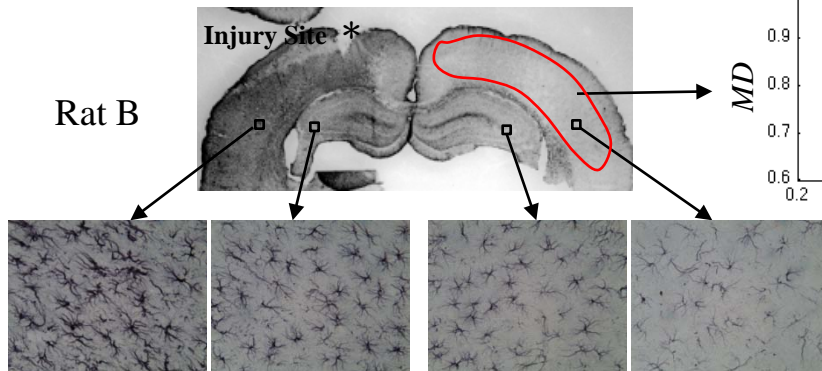
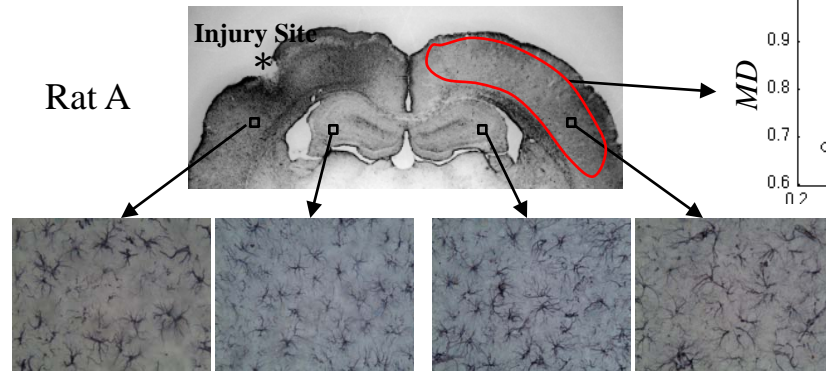
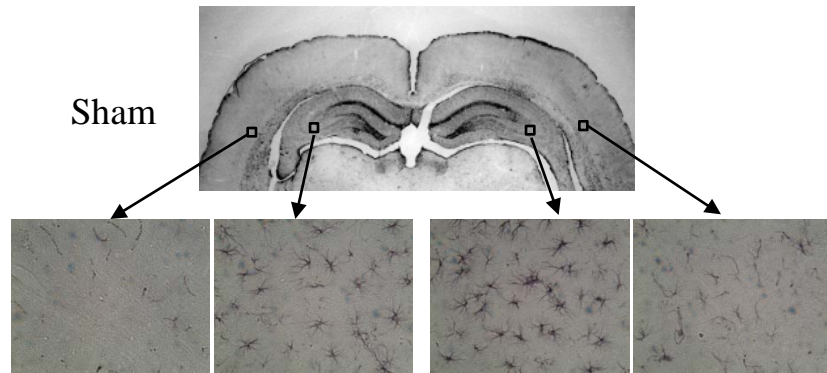
Injured site



\* :  $p < 0.05$

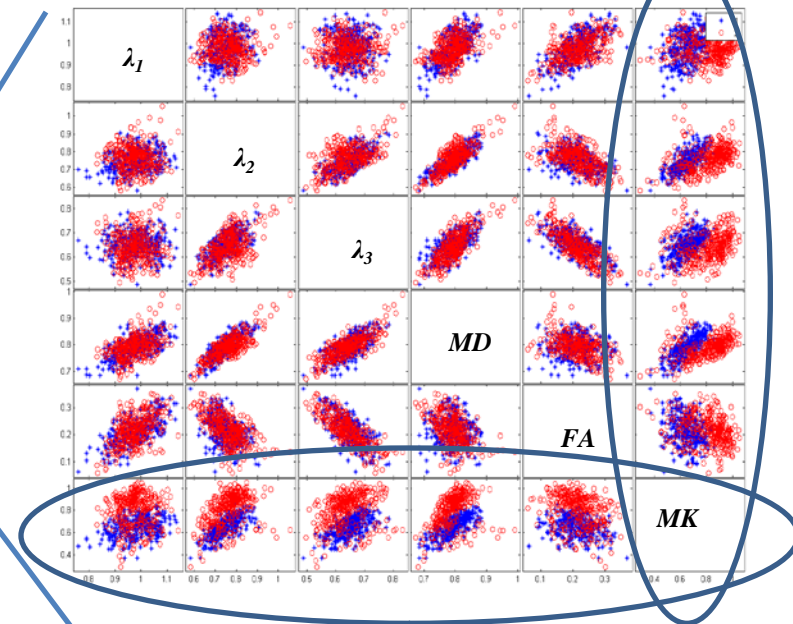
\*\*\* :  $p < 0.0005$

# Diffusion Kurtosis – Imaging Marker for Astrogliosis?



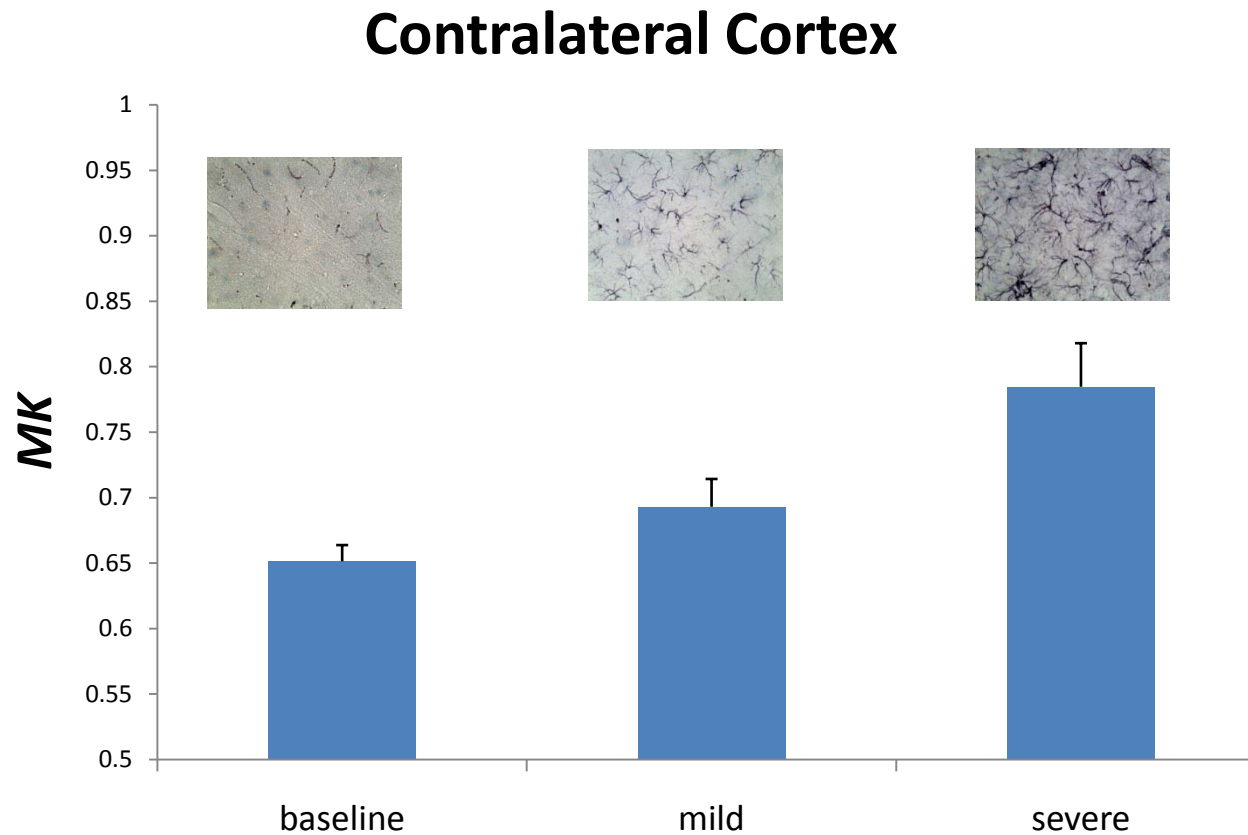
\* Baseline  
○ 7 day post injury

Pair-wise cluster plot



Blue: base line   Red: 7 day post injury

# Correlation between histology & MK



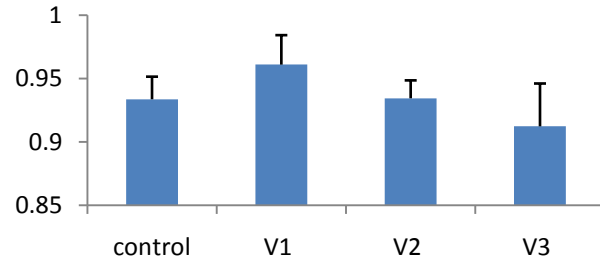
# Conclusion

- We observe a clear association of mean kurtosis with increased GFAP immunoreactivity.
- Mean Kurtosis is increased despite the fact that DTI parameters such as *MD* and *FA* were normal.
- Mean Kurtosis appears to be a sensitive marker for mild inflammatory responses, even in grey matter regions and may help in the management of secondary injury.
- Other biological factors (processes associated with neurodegeneration, microglia, etc.) can also affect mean kurtosis.
- Future studies will focus on understanding how these factors affect diffusion and kurtosis parameters.

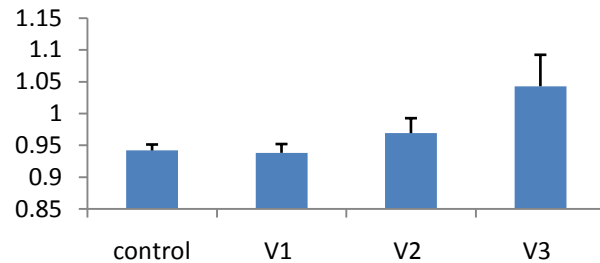
# Whole Brain DTI/DKI values from Whole Brain Grey/White matter

## White matter

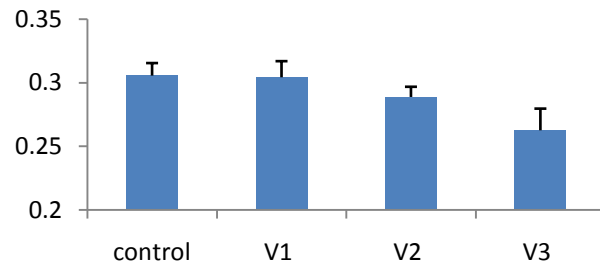
### MK mean



### ADC mean

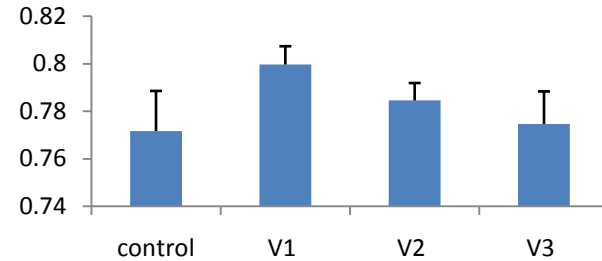


### FA mean

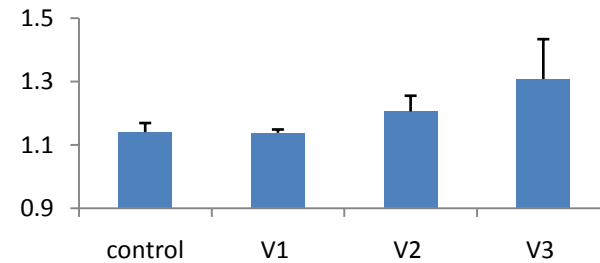


## Grey matter

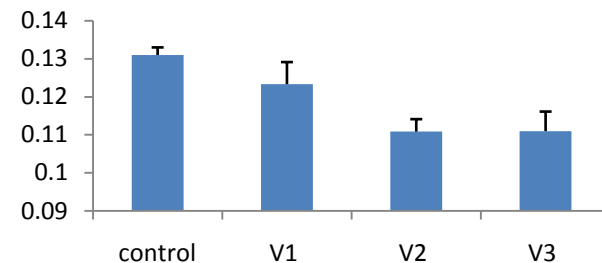
### MK mean



### ADC mean



### FA mean



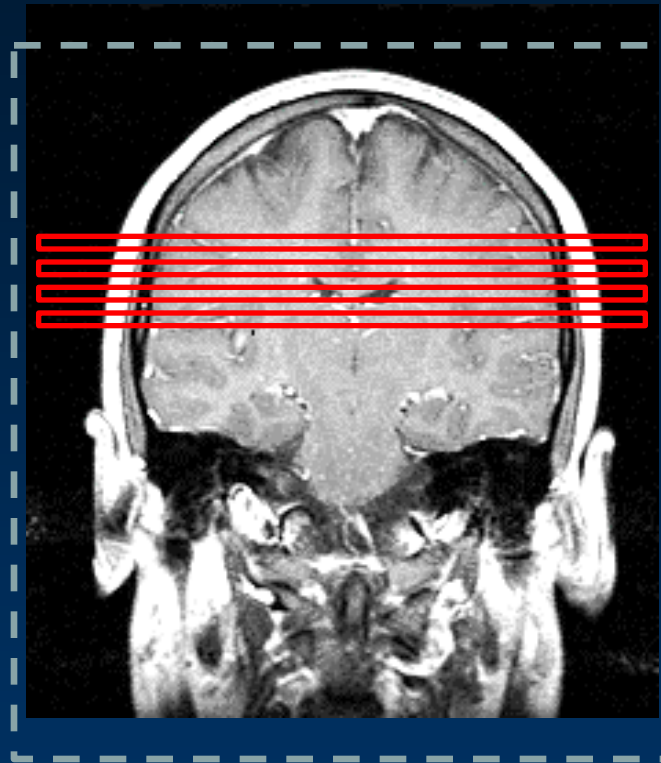
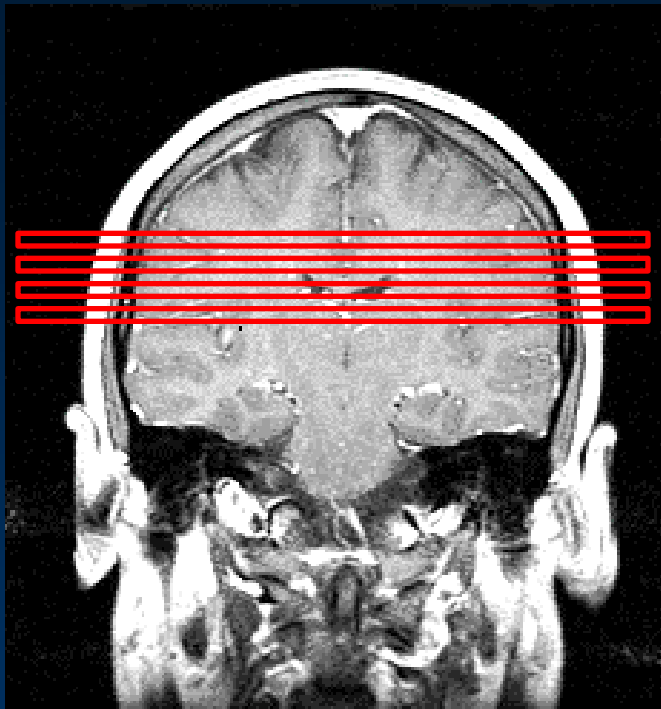
Control (n = 6), v1 (n = 13), v2 (n = 7), v3 (n = 3).

# Cerebral Blood Perfusion - Arterial Spin Labeling

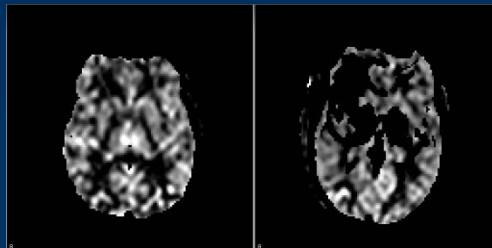
- Measures tissue perfusion
- Important to understand local tissue metabolic demands.
- Local tissue vulnerability
- Information on cerebral metabolic oxygen consumption,  $\text{CMRO}_2$



# Arterial Spin Labeling



*Spin  
Inversion  
tag*

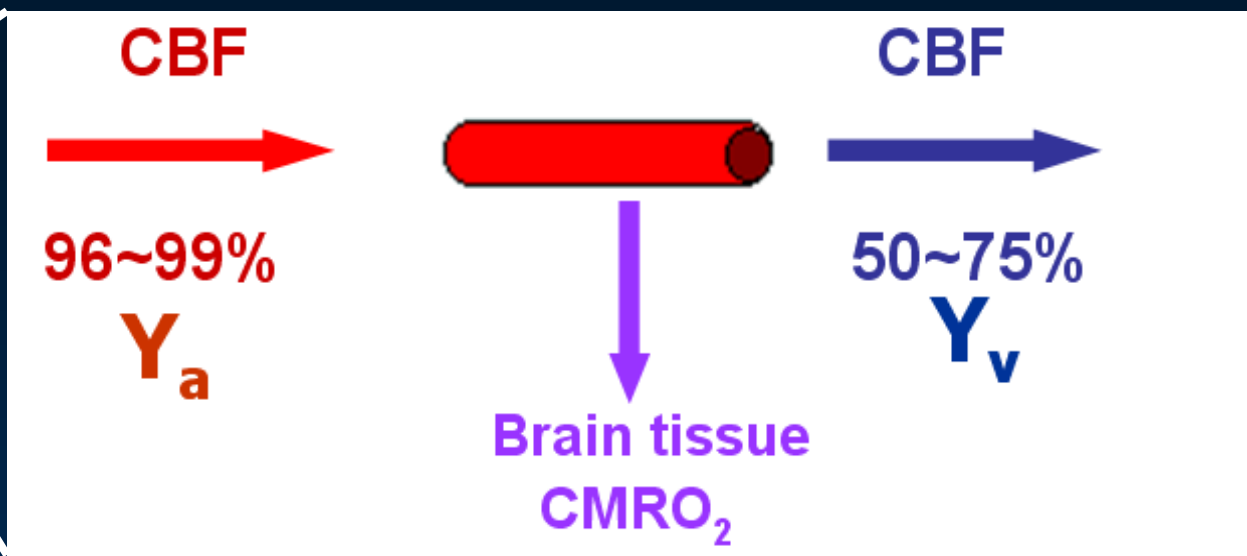
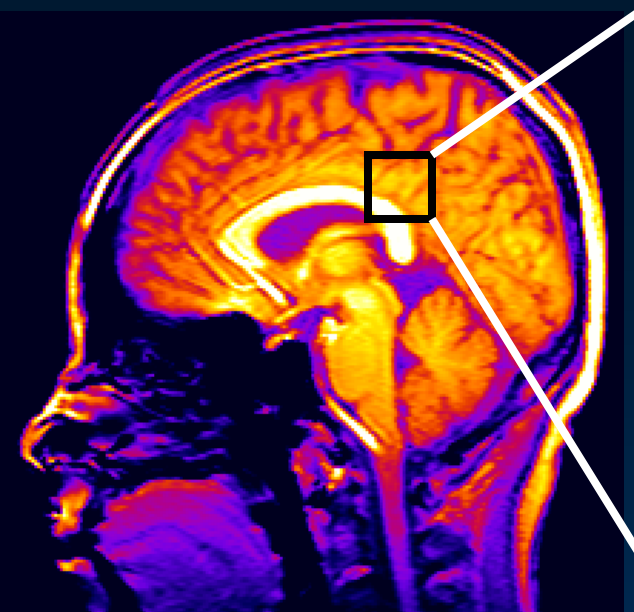


Normal  
subject

Severe  
TBI

Provides quantitative CBF

*Can we measure  $CMRO_2$ ?*



$$CMRO_2 \propto CBF \cdot (Y_a - Y_v)$$

Cerebral  
metabolic  
rate of  
oxygen

Phase  
contrast  
MRI

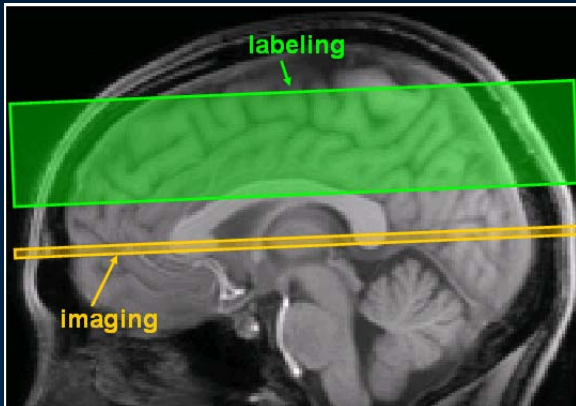
TRUST  
MRI

Pulse  
Oximeter

Brain:

- 2% of the body weight
- Uses 20% of the whole body's energy budget

# T<sub>2</sub>-Relaxation-Under-Spin-Tagging (TRUST) MRI technique



Effective TE (ms)

0

40

80

160

eTE = 0 ms

eTE = 40 ms

eTE = 80 ms

eTE = 160 ms

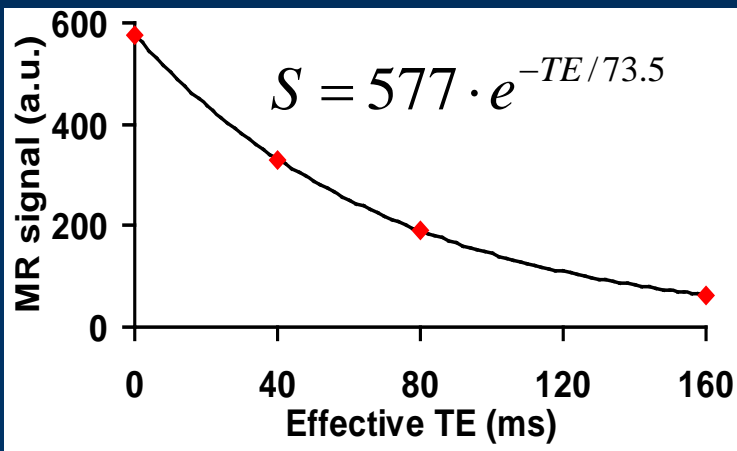
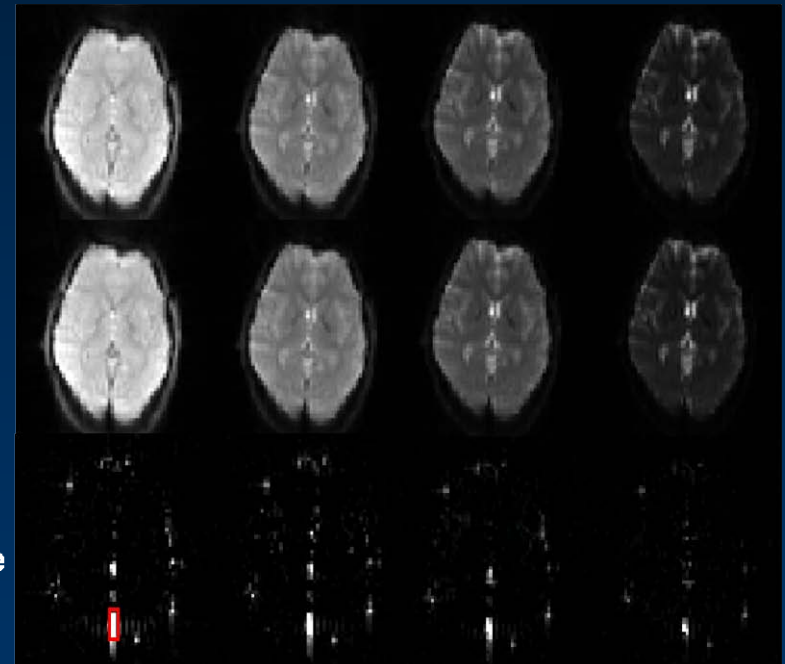
C

Control

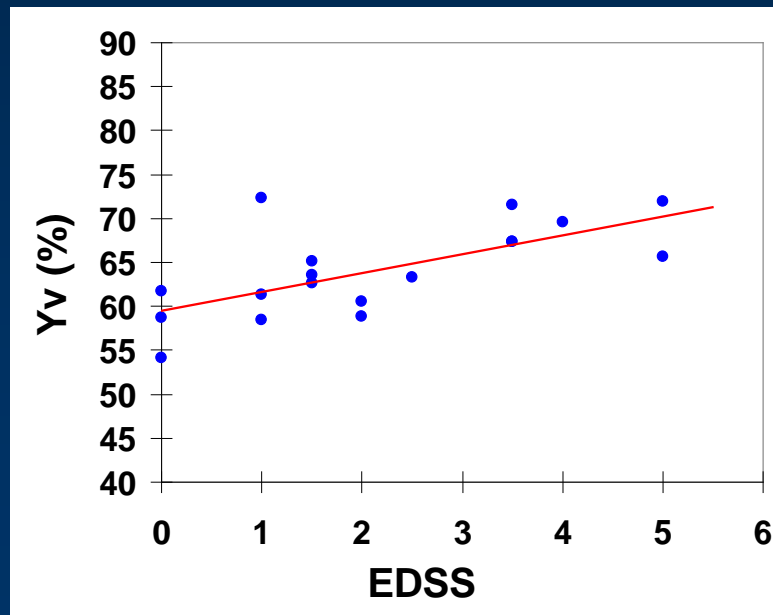
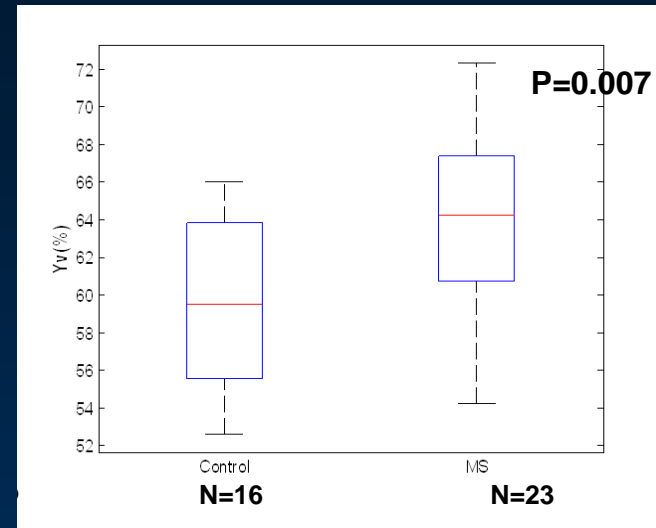
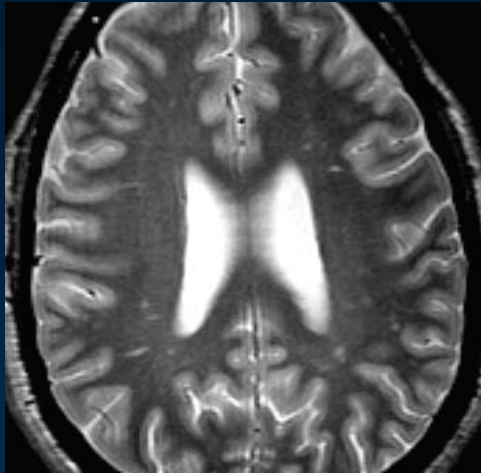
L

Labeled

C - L Difference



# Patients with relapsing-remitting Multiple Sclerosis have paradoxically high venous oxygenation



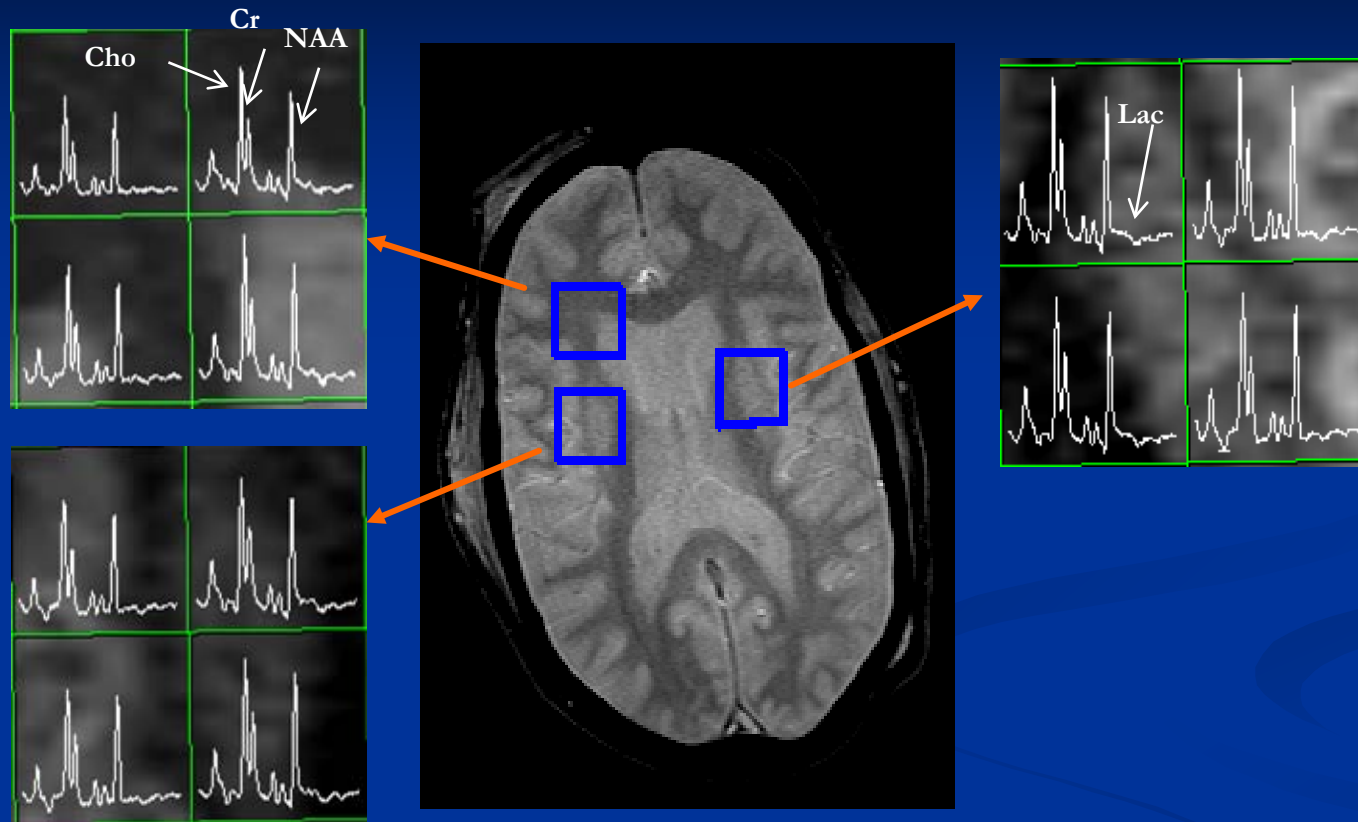
*Higher venous oxygenation relates to greater disability among MS patients*

# **‘Whole Brain’ MR Spectroscopic Imaging**

# Why Use MRS for TBI?

- ❑ Lack of objective measures for injury assessment and outcome prognosis
  - Particularly for mild injury, ~75% of subjects
  - Limitations of structural imaging
    - frequently shows no findings (DAI not visible); little correlation between imaging findings and outcome
  - Functional Imaging, e.g. PET, MEG
    - show greater sensitivity, but their availability is limited
- ❑ Previous studies
  - MRS studies have shown decreased NAA, indicating neuronal loss, and correlations with injury and outcome;
    - however, these studies primarily looked at moderate to severe injury and used older acquisition methods.

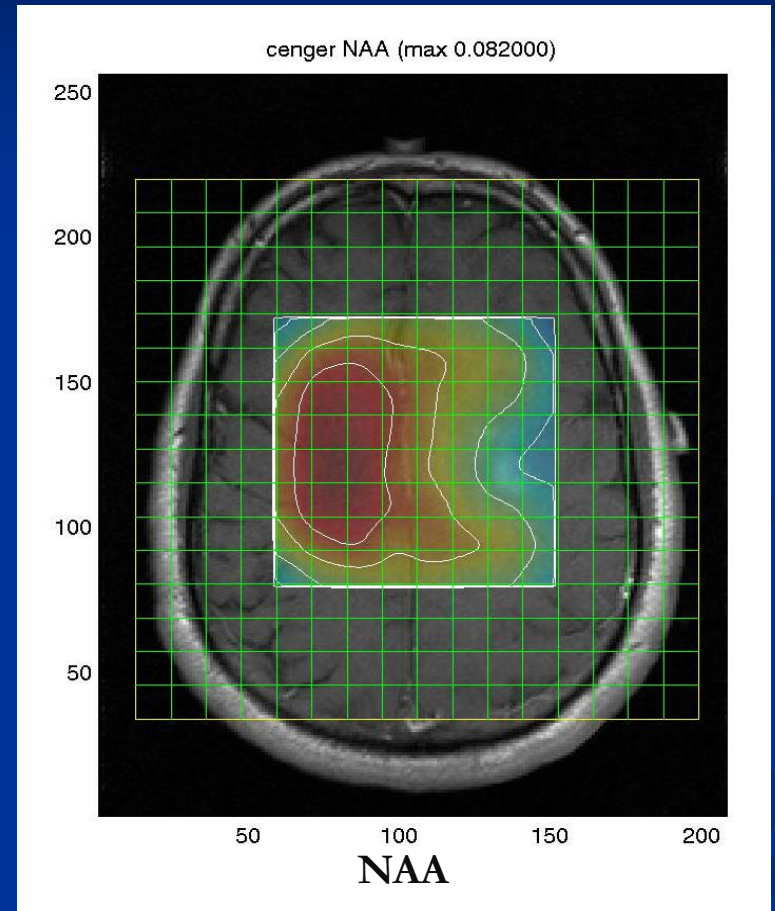
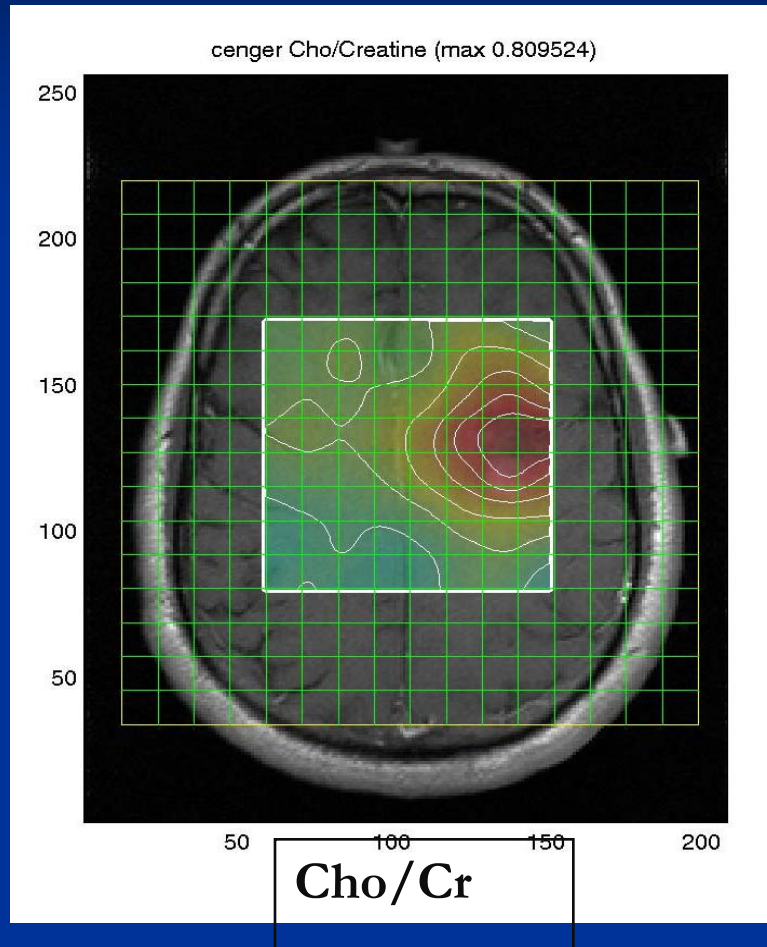
# Magnetic Resonance Spectroscopy



**Spectra from a motor vehicle accident victim with a GCS of 5. The genu, internal & external capsule, and basal ganglia show a general decrease in NAA and an increase in the Cho/Cr ratio.**



# Limitations of 3D-Spectroscopy

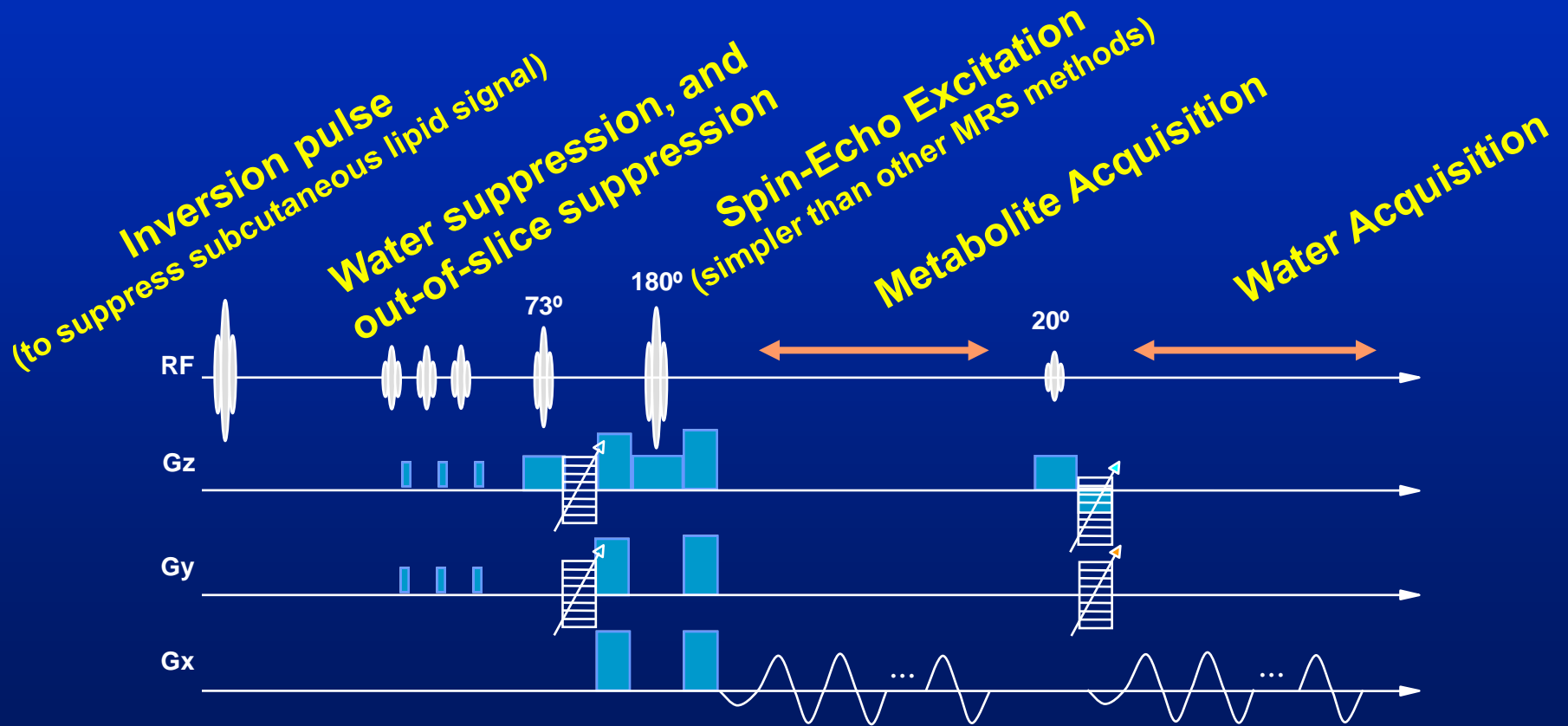


- Limited coverage
- Can miss crucial areas such as the gray-white junctions

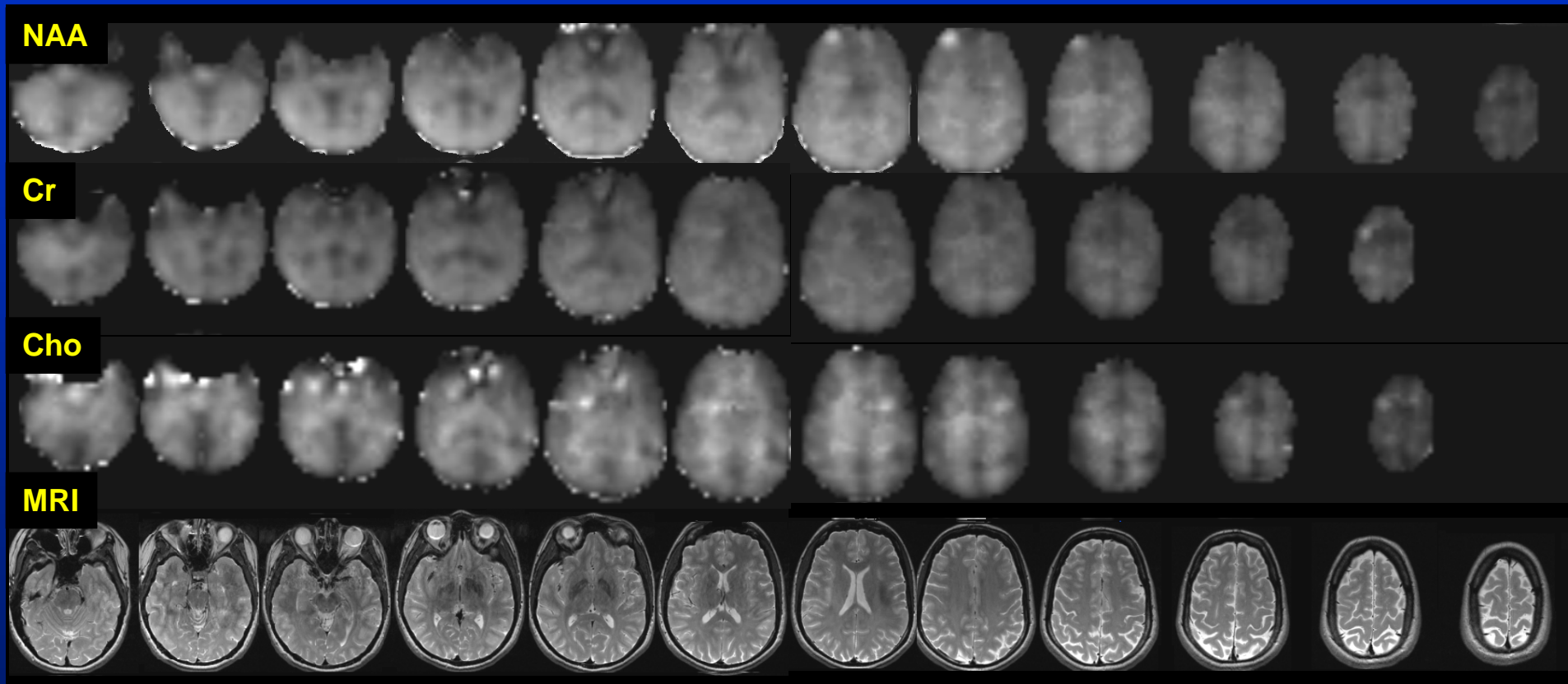


# Volumetric SI

- Echo-Planar SI with interleaved water reference

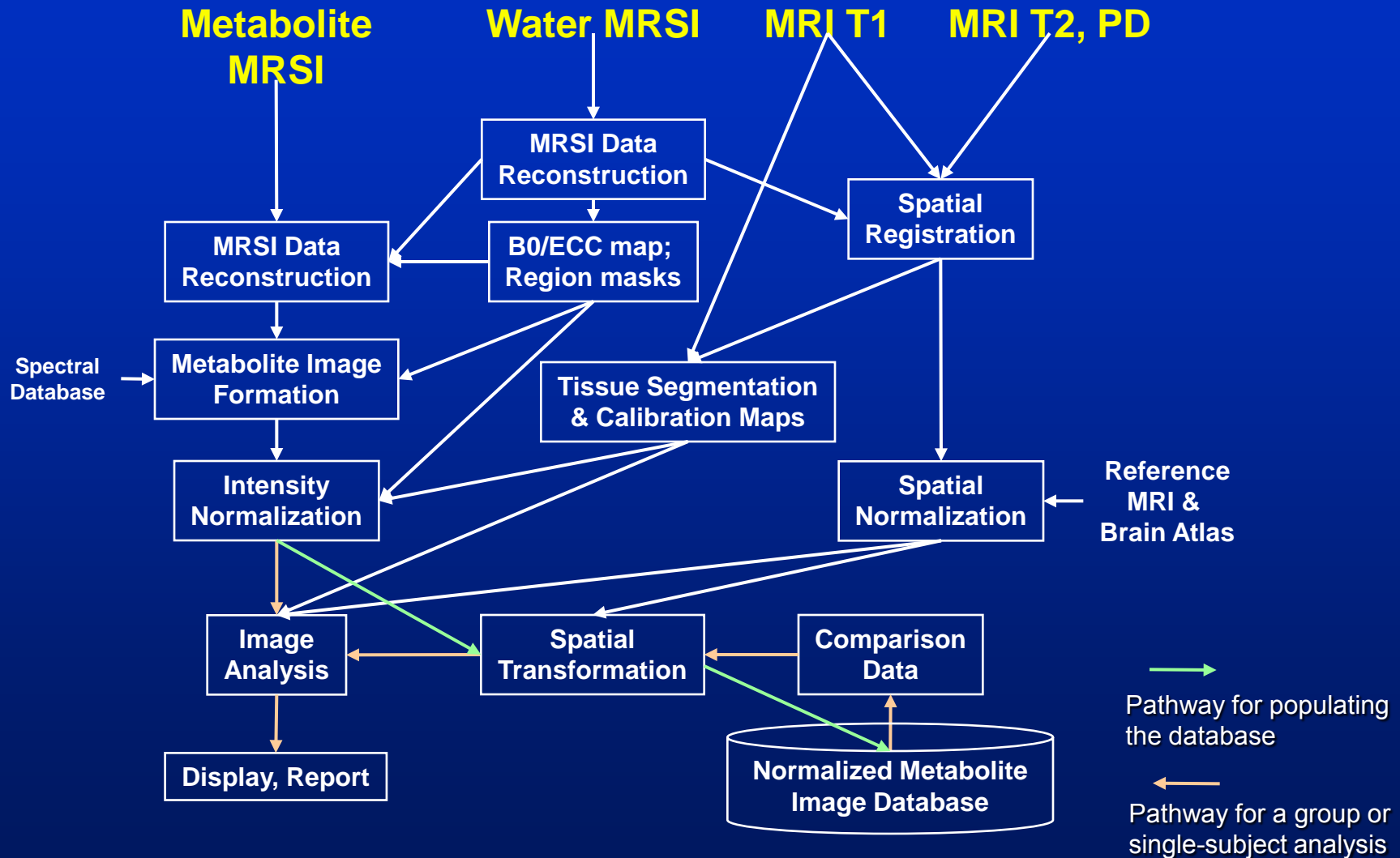


# Volumetric $^1\text{H}$ EPSI Example

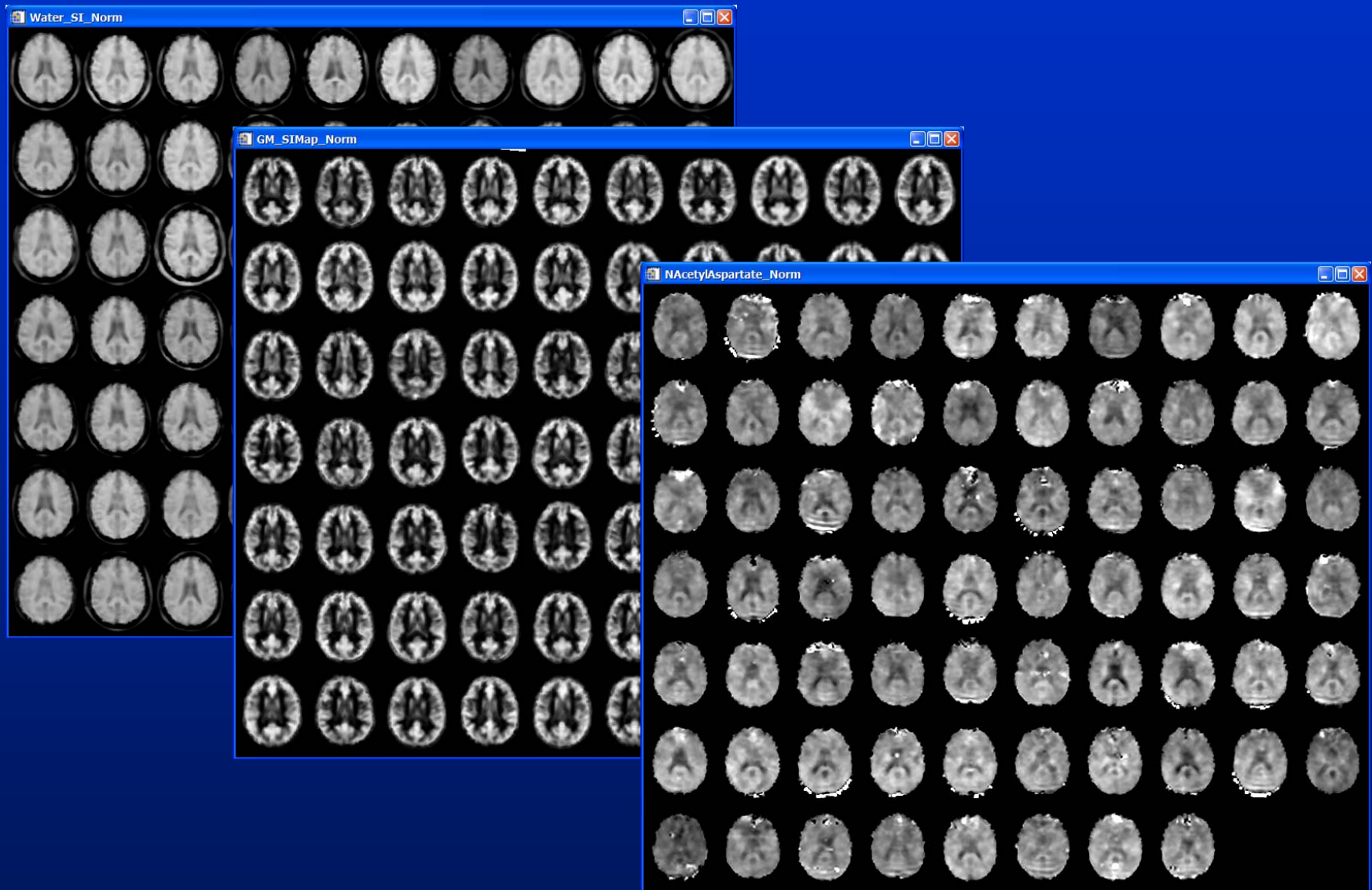


Volumetric, whole-brain EPSI,  
50x50x18 acquisition matrix, 26 min.  
(Siemens 3T Trio, TE=70 ms, TR = 1710 ms)

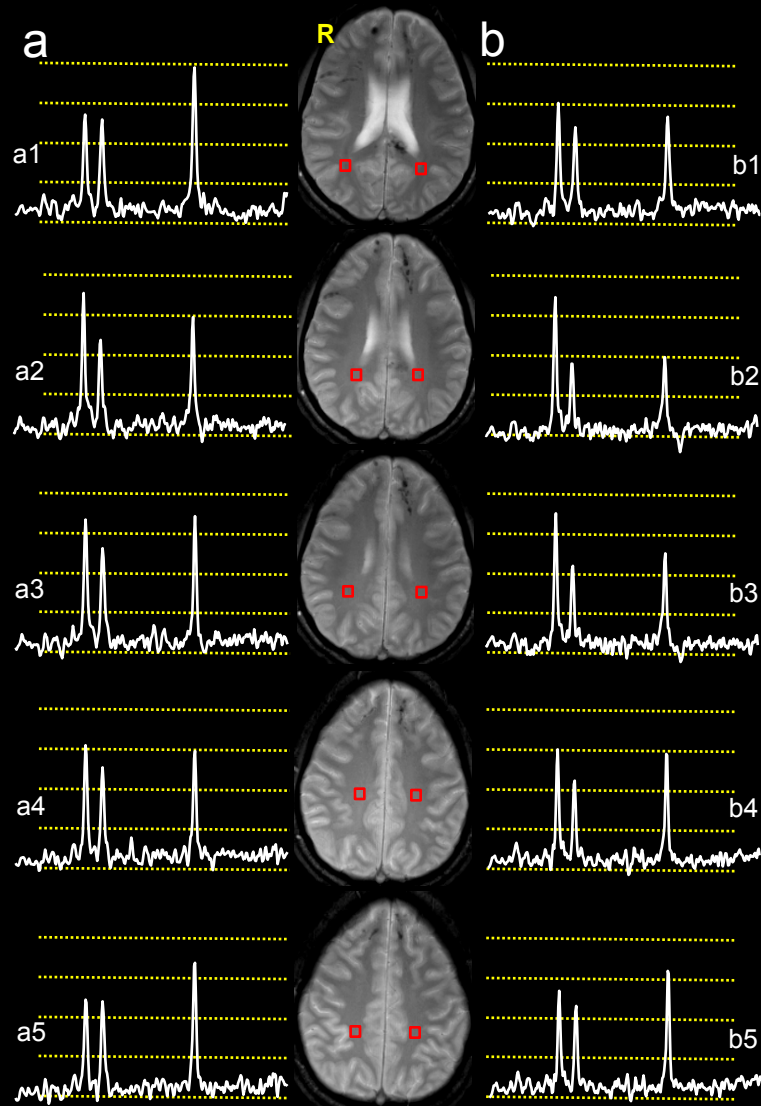
# MRI+MRSI Processing & Analysis – The MIDAS Package



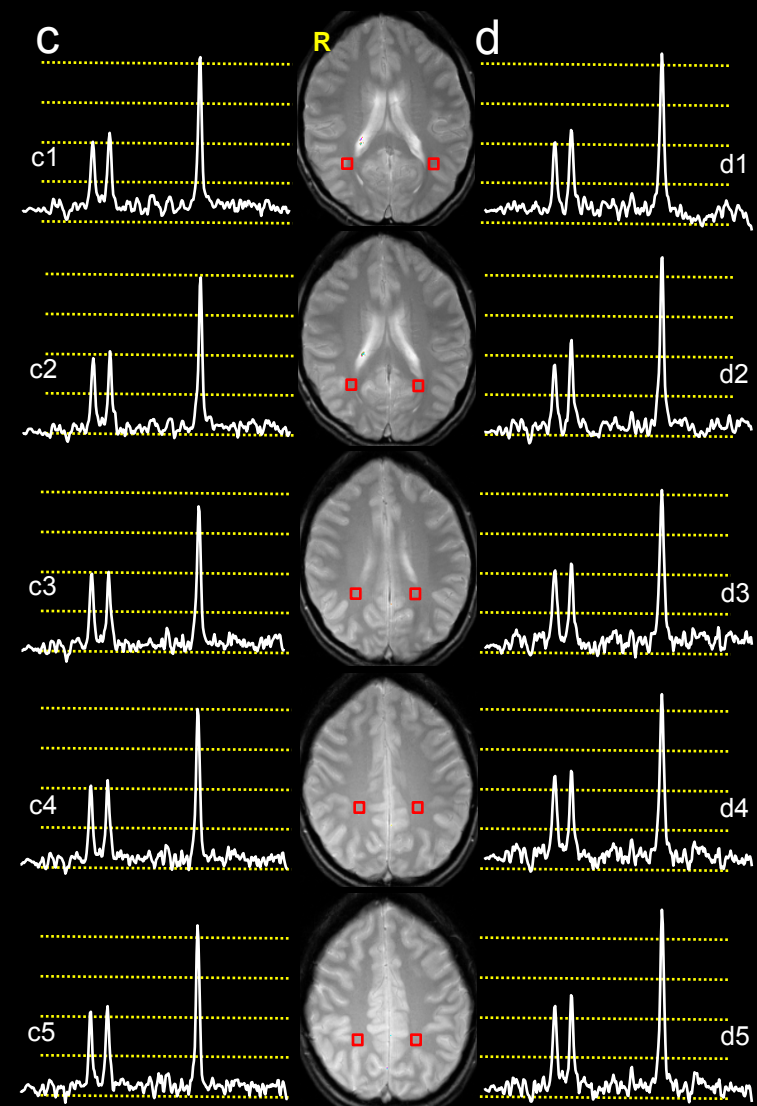
# Map All Data to Standard Space



# Comparisons between the brains with TBI and Normal



22 year old male  
Mild TBI, MVA, GCS13, contusion, SDH

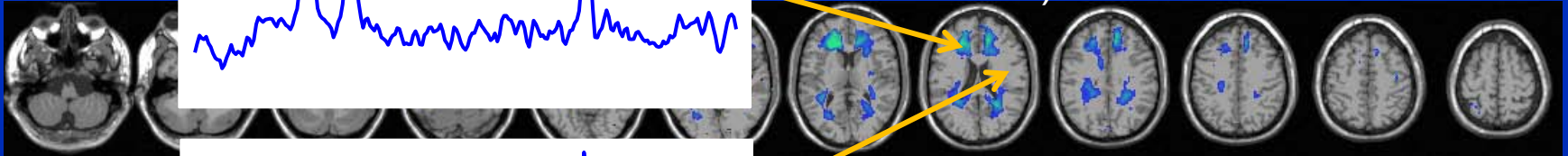


23 y old female  
Control

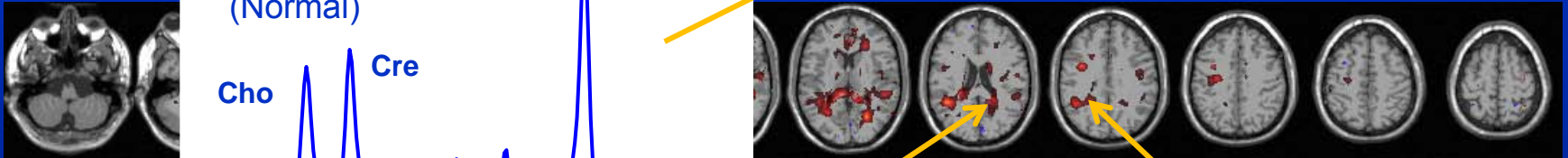


# Magnetic Resonance Spectroscopy

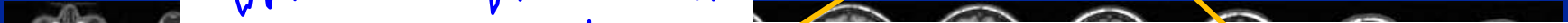
NAA z-score map



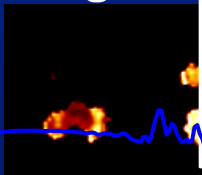
Cho z-score map



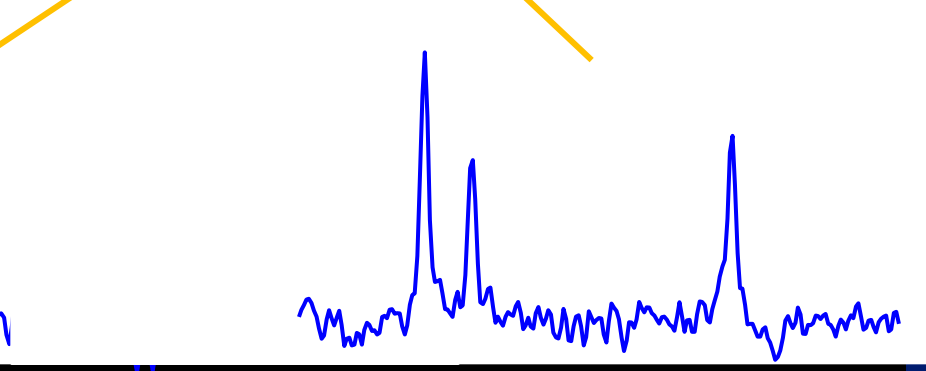
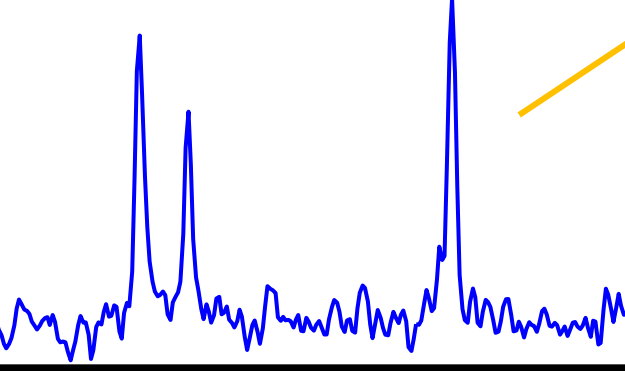
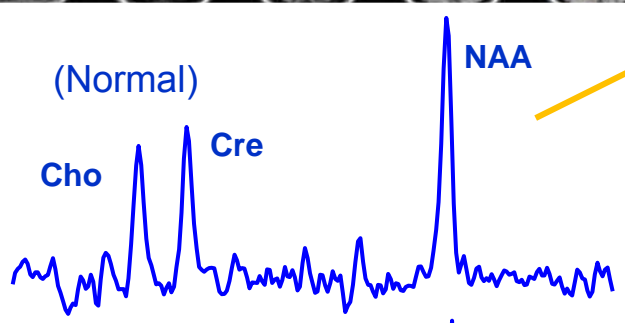
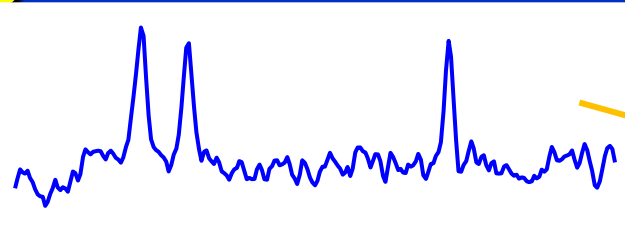
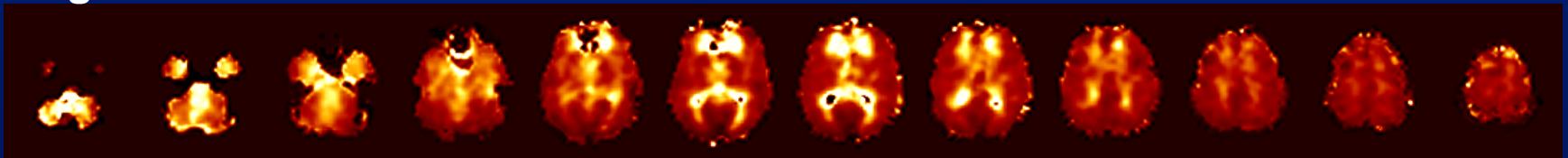
Cho/NAA z-score map



NAA image



Cho image

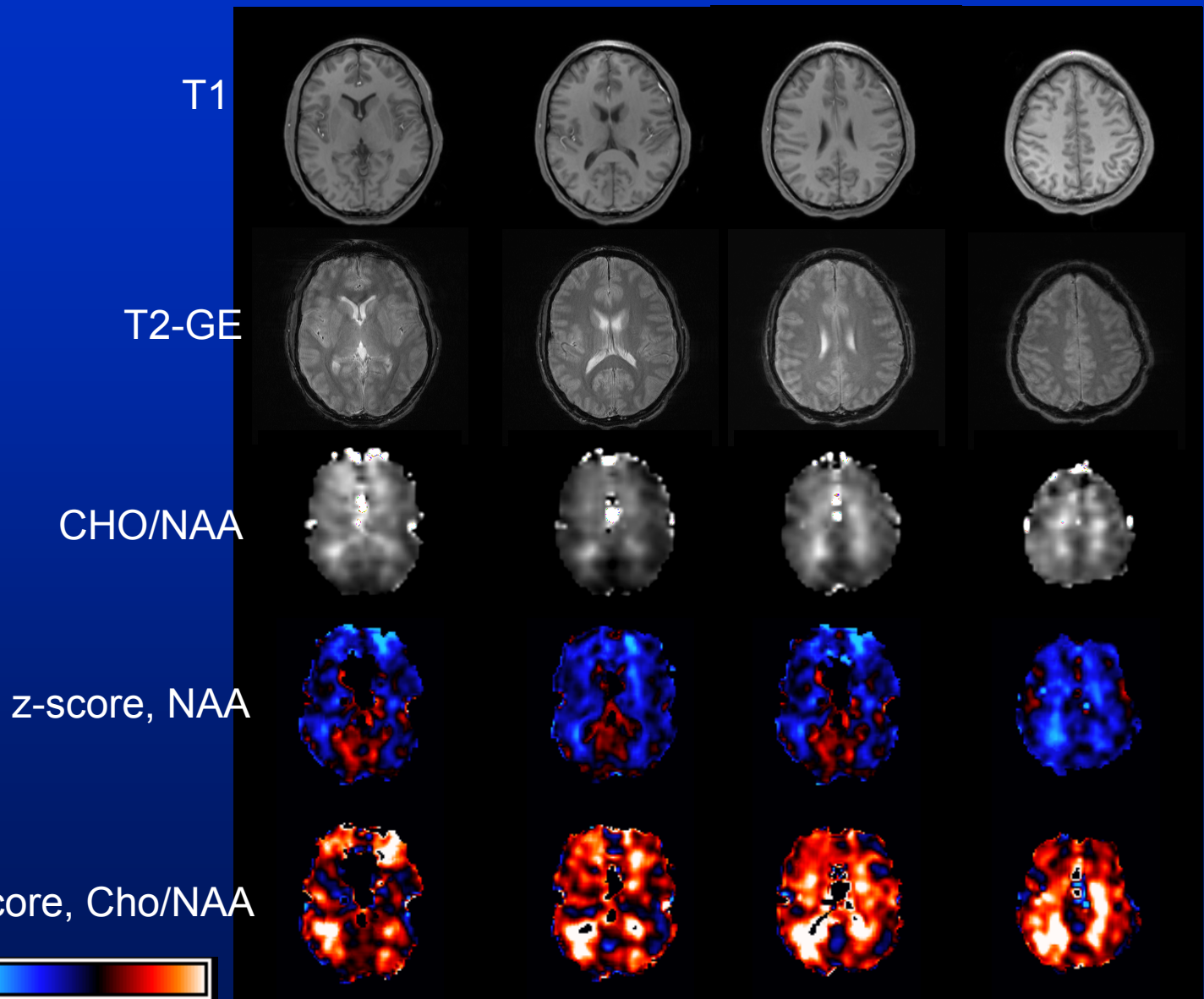


GCS 13, MVA, 52 days after injury

# Magnetic Resonance Spectroscopy

Male, 21 years old  
Motor vehicle  
accident  
GCS = 15  
Scanned after 22  
days

MRI findings:  
Relatively minor  
bifrontal subacute  
cortical and white  
matter contusions  
No diffuse axonal  
injury (DAI)

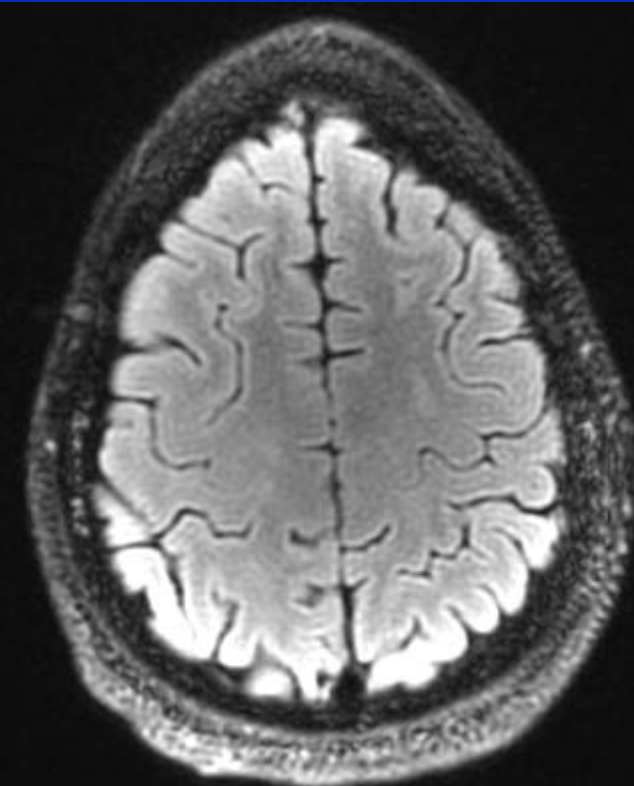


# Whole Brain Spectroscopy - Summary

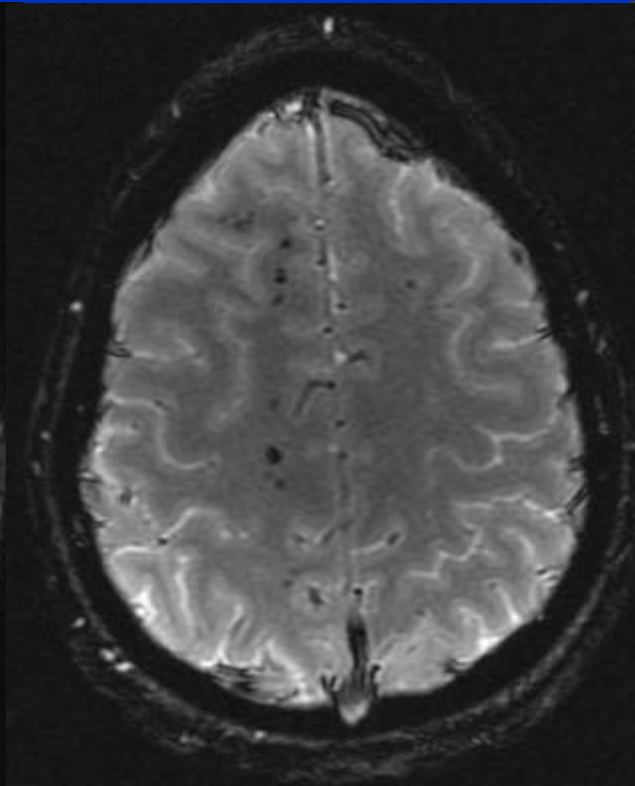
- ❑ Widespread metabolic alterations observed, even for mild TBI (GCS 14, 15)
  - $\uparrow$ Choline and  $\downarrow$ NAA
  - Primarily in white matter
- ❑ Significant improvement in coverage over standard 3D-CSI techniques
- ❑ Correlations between MRSI measures and cognitive performance
- ❑ Future developments will reduce data acquisition time to 15 min using 32 channel coils



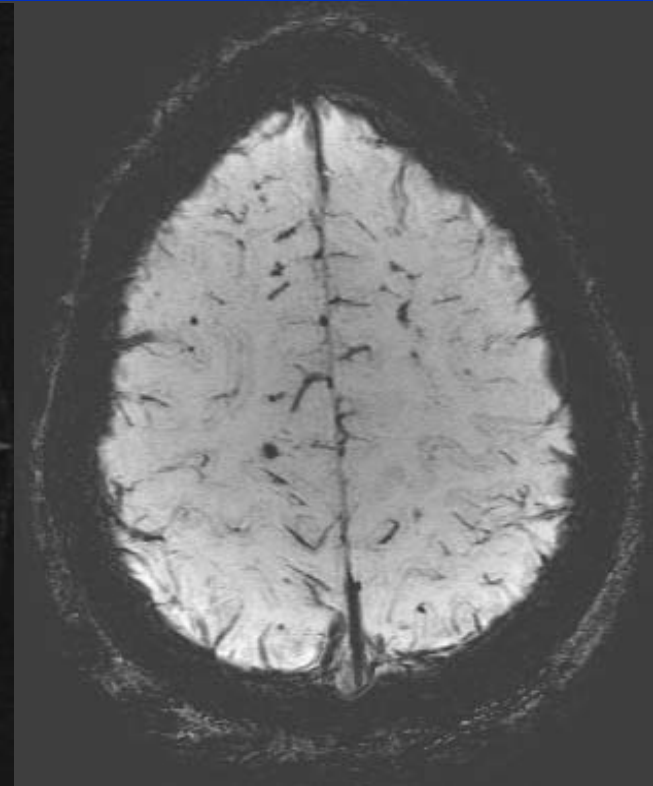
# TBI Microhemorrhage



T2 FLAIR



GRE



SWI

- 22 yo male, 40 days after IED blast, Dx mild TBI
- No recollection of events, some retrograde amnesia
- Symptoms: balance problems, spinning sensation, short-term memory loss, diplopia

*Courtesy, Dr. Gerard Riedy,  
National Capital Neuroimaging Consortium*

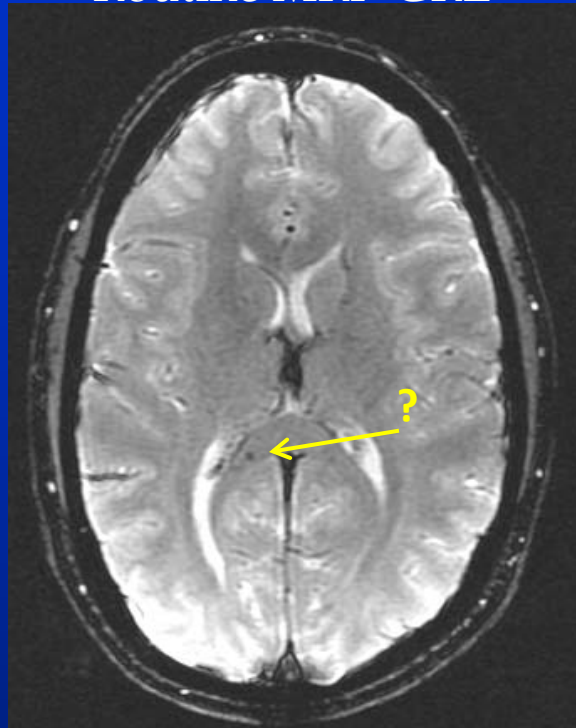
# TBI Microhemorrhage

CT



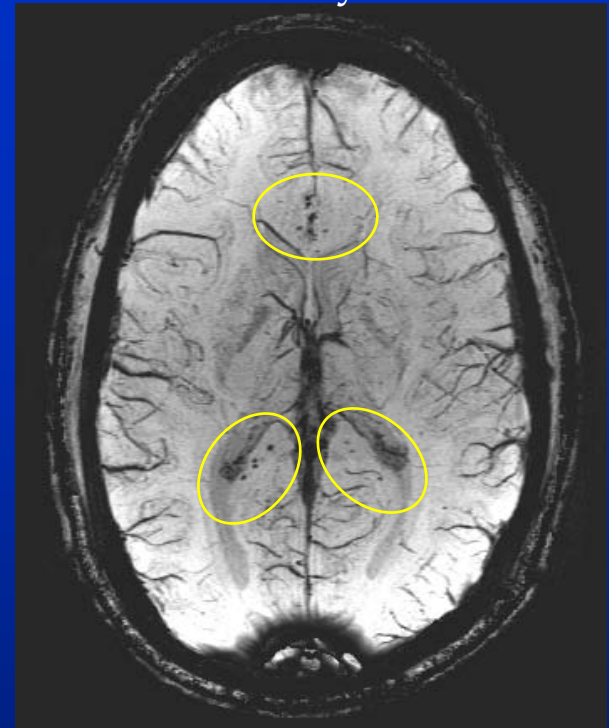
Read as Normal

Routine MRI- GRE



Possible Lesion  
Corpus Callosum

TBI Study- SWI



Multiple Lesions Detected

- 24 yo male, one month after IED blast, Dx mild TBI
- Knocked out of vehicle and was unresponsive
- Symptoms: balance problems, memory loss, hearing loss, sleep disturbances

*Courtesy, Dr. Gerard Riedy,  
National Capital Neuroimaging Consortium*

# Resting State Functional MRI

# Case Studies

## Patient A

49 year old Female

Fall

Negative Head CT

Score on Rivermead  
Symptoms:

Initial = 39

1 month = 34

## Patient B

20 year old Male

Assault

Positive Head CT

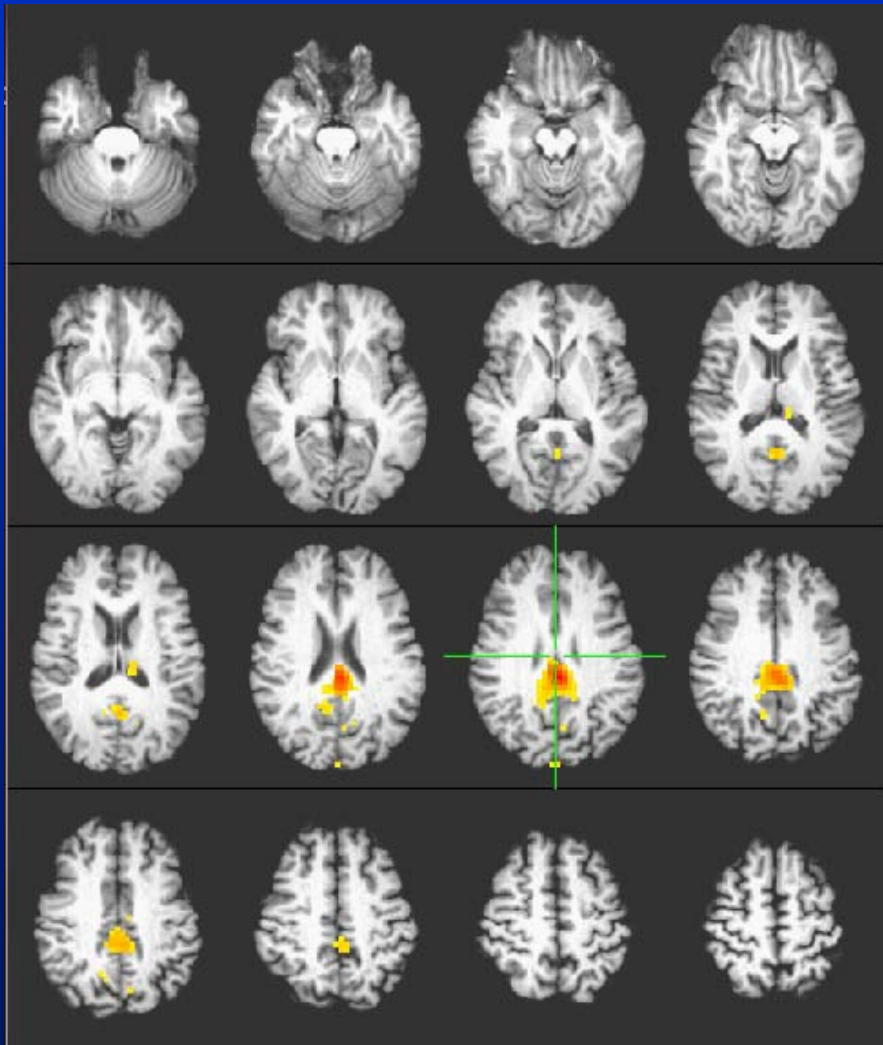
Score on Rivermead  
Symptoms:

Initial = 1

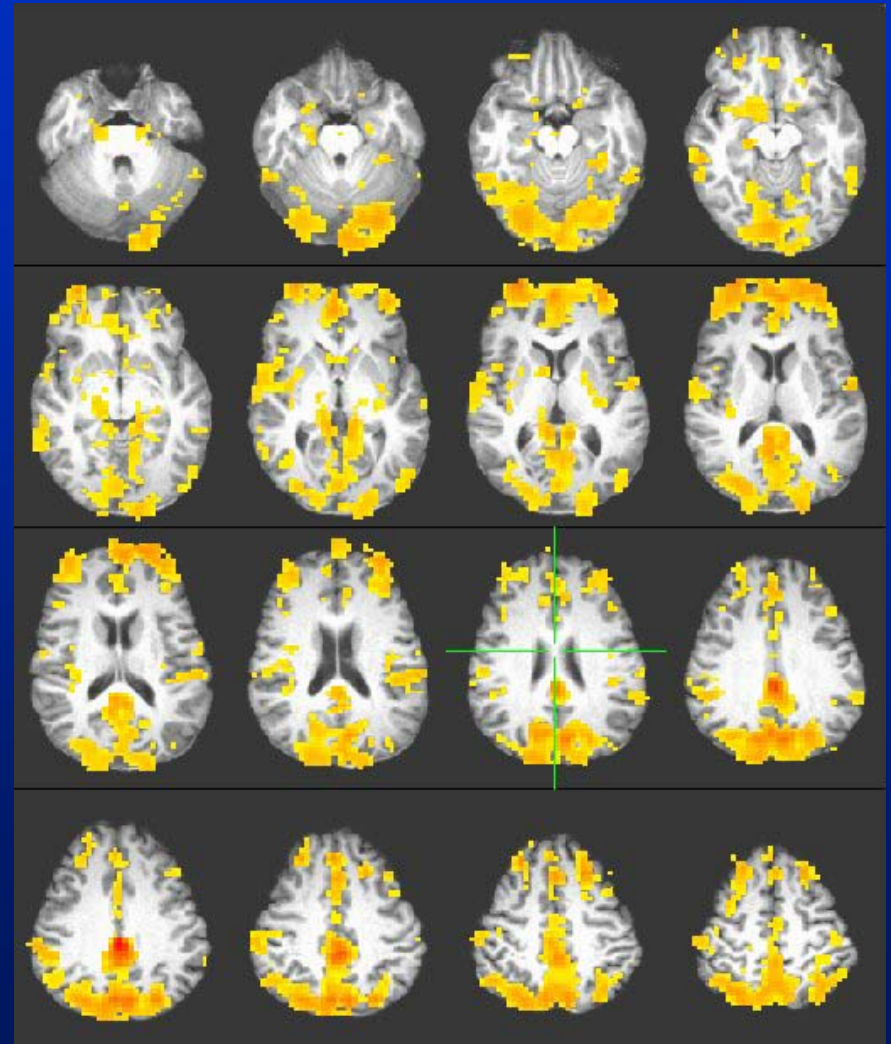
1 month = 1

# Default Mode Network Initial Scan

Patient A



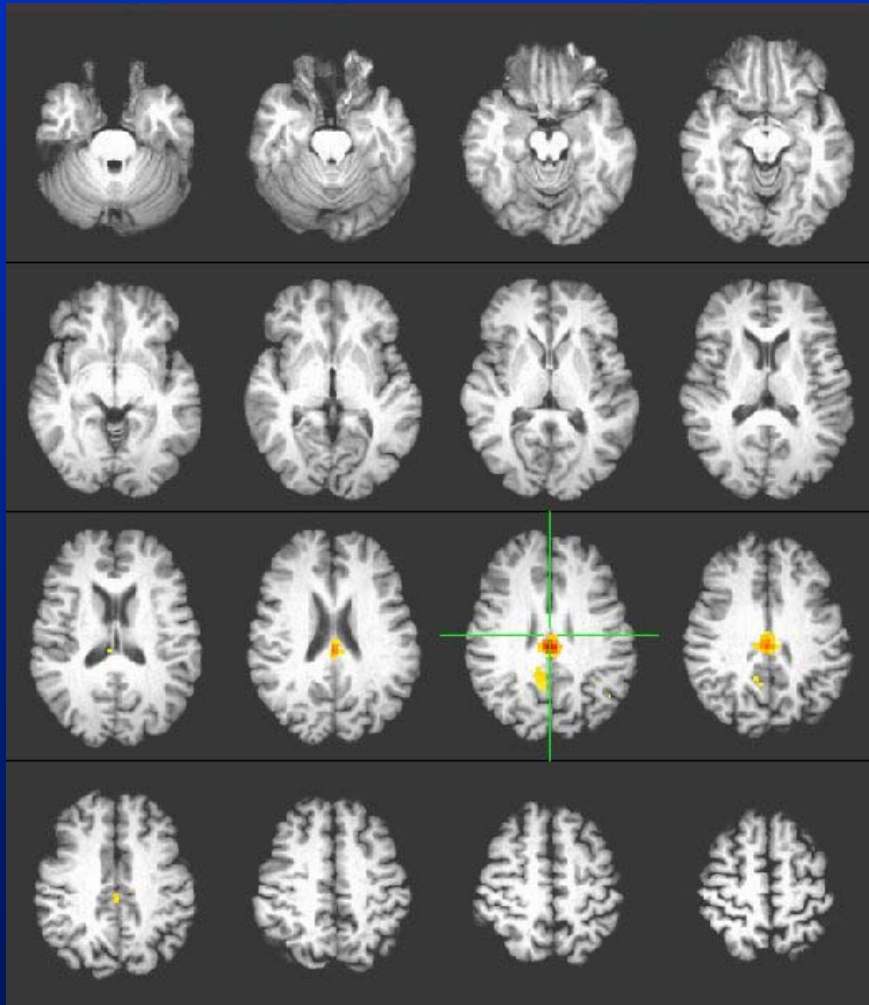
Patient B



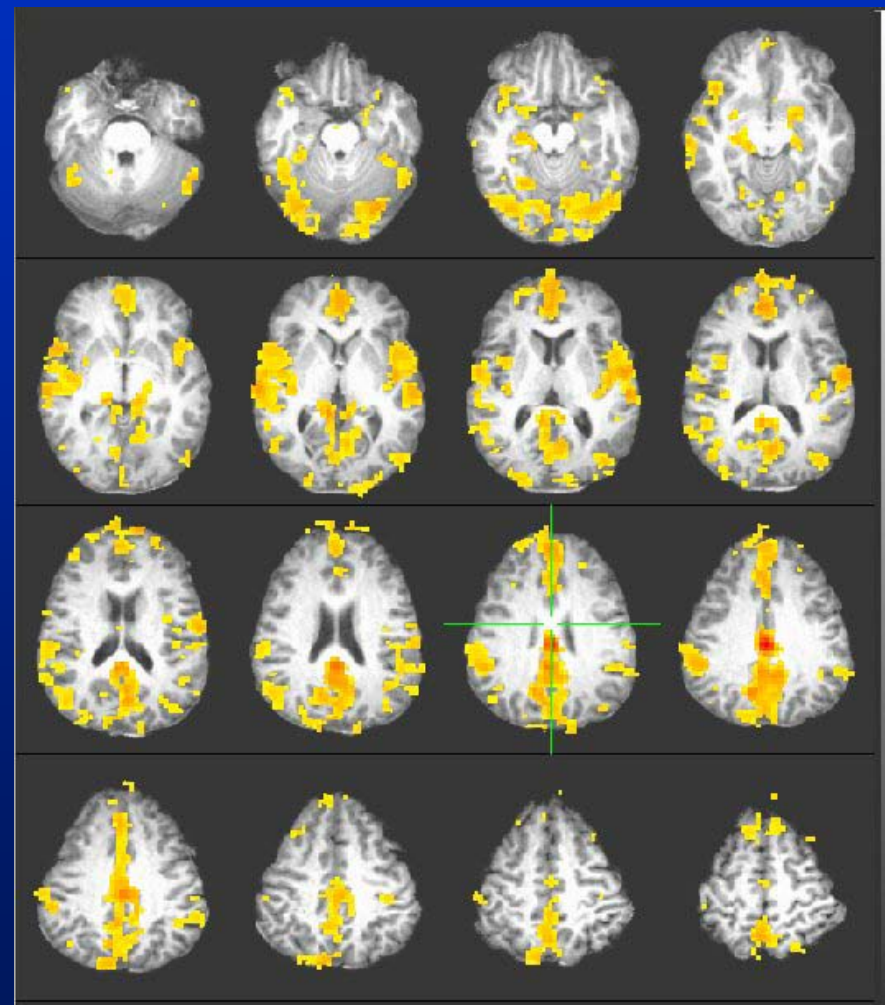


# Default Mode Network 1 month

Patient A

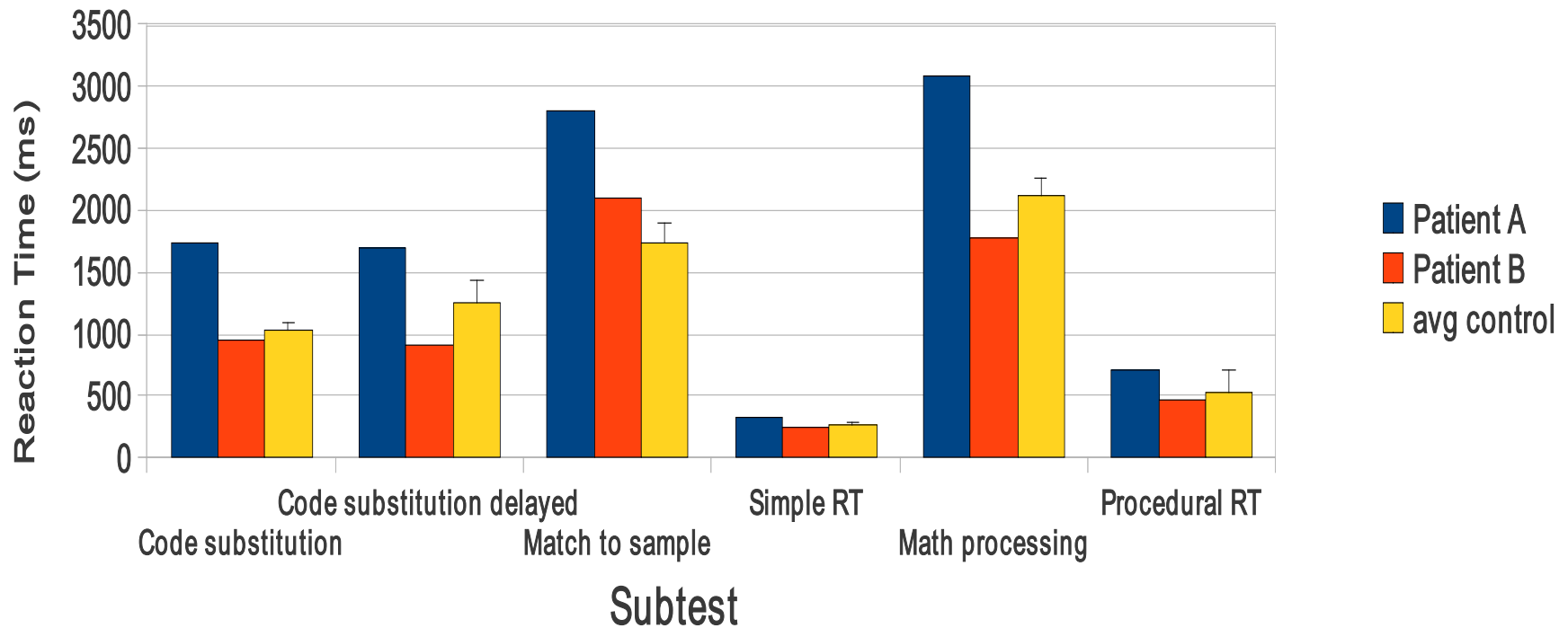


Patient B



# Default Mode Network

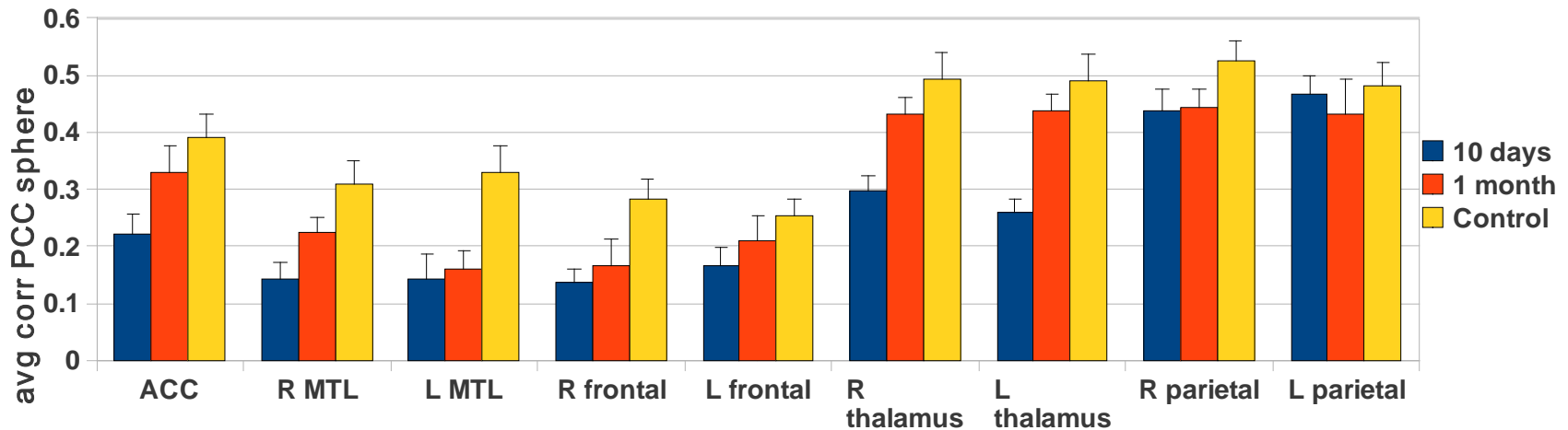
## ANAM Reaction Times at 1 Month



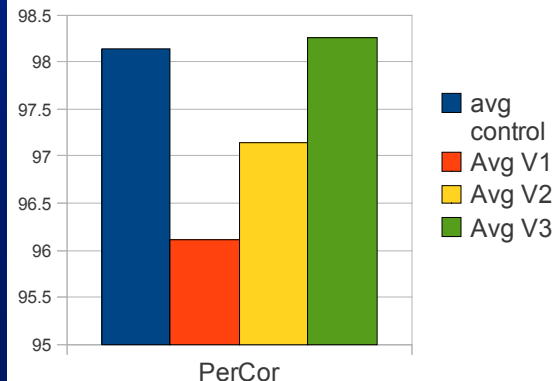
- While Patient A had negative head CT, & conventional MR, performance on ANAM was worse at 1 month.
- Patient A had significantly lower functional connectivity within the DMN over 1 month
- Changes in DMN may be better predictor of the clinical status of patient

# Default Mode Network - Group Analysis for mild TBI

DMN Correlations



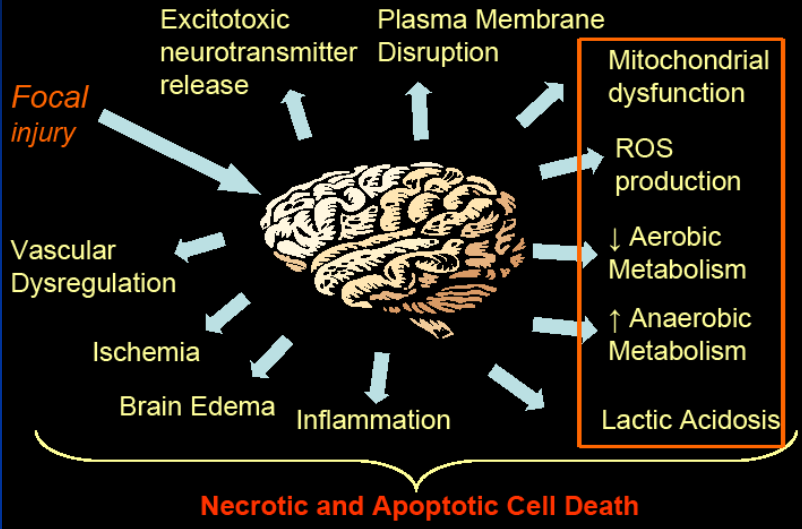
Code Substitution





# Summary

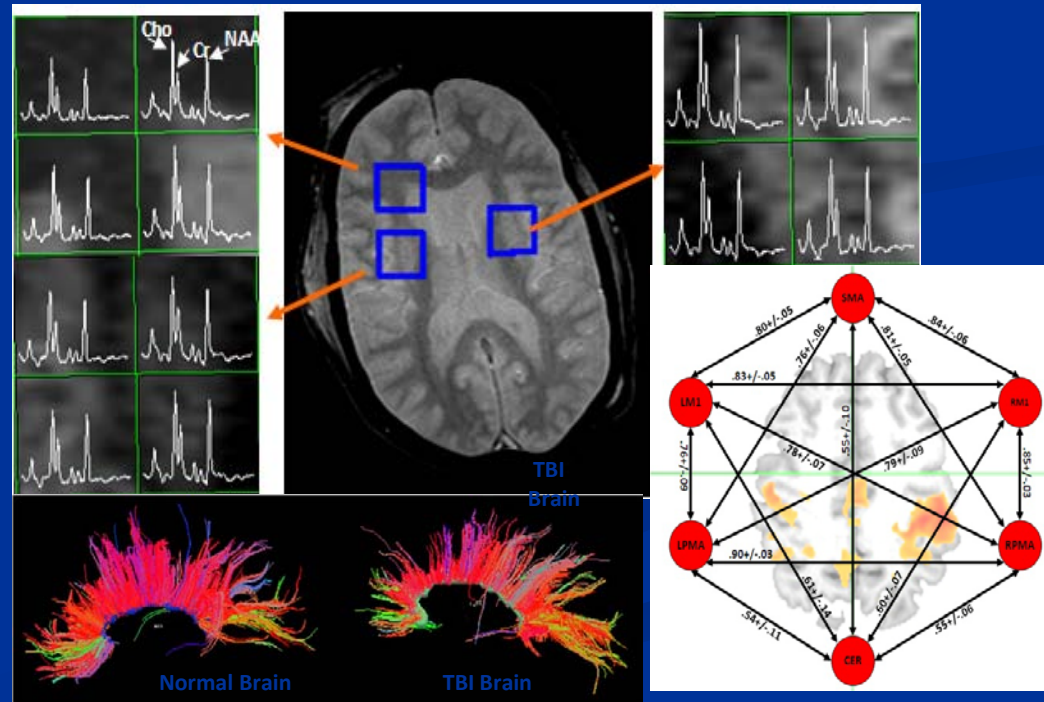
## Traumatic brain injury is complex



Advanced MR imaging techniques allow for a quantitative and comprehensive assessment of TBI patients non-invasively.

A single incident such as TBI that can take on variable course can benefit from the biophysical, biochemical, and vascular assessments offered by the advanced imaging techniques

Multiparametric approaches using various MRI techniques complemented by other imaging modalities such as PET, EEG, and MEG are likely to provide better insights into the accurate characterization of TBI and optimal clinical management of the patient.



Anatomic, Spectroscopic & Functional connectivity in TBI

# Acknowledgements

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U.S. Army W81XWH-08-1-0725; ONR N000141010886

# Core for Translational Research in Imaging @ Maryland (C-TRIM)



**Thank You!**

Manuscript Number:

Title: Prognostic Value of Diffusion Tensor Imaging Parameters in Severe Traumatic Brain Injury

Article Type: Article

Corresponding Author: Dr Rao P Gullapalli, Ph.D., MBA

Corresponding Author's Institution: University of Maryland Baltimore

First Author: Joshua Betz

Order of Authors: Joshua Betz; Jiachen Zhuo, MS; Anindya Roy, Ph.D.; Kathirkamanathan Shanmuganathan, MD; Rao P Gullapalli, Ph.D., MBA

#### Abstract: Background

To determine the relationship between diffusion tensor imaging (DTI) measures and the clinical status of severe traumatic brain injury (TBI) patients both at the time of MRI and their discharge to acute TBI rehabilitation and assess its prognostic value.

#### Methods

Patients (n=79) admitted to the trauma center with severe closed head injury were retrospectively evaluated, after approval from the institution's IRB, to determine the prognostic value of DTI measures. The relationship of DTI measures including apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial ( $\lambda_{||}$ ), and radial diffusivity ( $\lambda_{\perp}$ ) from the whole brain white matter, internal capsule, genu, splenium, and body of the corpus callosum were assessed with neurological status at MRI and at discharge to acute TBI rehabilitation.

#### Findings

Whole brain white matter averages of ADC,  $\lambda_{||}$ , and  $\lambda_{\perp}$  and their coefficient of variation (CV) were significantly correlated with the Glasgow Coma Scale (GCS) on the day of MRI. Regionally, the average  $\lambda_{||}$  was significantly correlated with GCS in the internal capsule and corpus callosum, on the day of MRI. Outcomes were associated with whole brain white matter averages of ADC and  $\lambda_{||}$  and the CVs of FA, ADC,  $\lambda_{||}$ , and  $\lambda_{\perp}$ , and the averages and CVs of FA and  $\lambda_{||}$  in all corpus callosum regions. Regional and global DTI measures improved the prognostic models, when adjusted for admission GCS and age ( $p < 0.05$ ).

#### Interpretation

Whole brain white matter and regional DTI measures are sensitive markers of TBI and correlate with neurological status both at MRI and discharge to rehabilitation. Addition of DTI measures adjusted for age, gender, and admission GCS significantly improved prognostic models.

#### Funding

This work was partially supported by a grant from the DOD (Award # W81XWH-08-1-0725)

# **Prognostic Value of Diffusion Tensor Imaging Parameters in Severe Traumatic Brain Injury**

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Kathirkamanathan Shanmuganathan, MD<sup>2</sup>, Rao Gullapalli, Ph.D.<sup>1,2</sup>

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### **Advances in Knowledge:**

Global and regional white matter diffusion tensor imaging (DTI) parameters are strongly associated with patient outcomes in severe traumatic brain injury (TBI).

Fractional Anisotropy (FA) was the most sensitive marker in analyses of regions of interest in the corpus callosum and internal capsule, while apparent diffusion coefficient (ADC) was more sensitive in detecting global changes in white matter.

Changes in both FA and ADC appear to be driven primarily by reductions in axial diffusivity ( $\lambda_{\parallel}$ ), with decrements in  $\lambda_{\parallel}$  consistently associated with poor neurological status upon discharge to TBI rehabilitation.

The variability in DTI parameters also provides information about patient outcomes, and the coefficient of variation is able to synthesize information about both the mean and the variability of DTI parameters both regionally and globally.

## **ABSTRACT**

### **Background**

To determine the relationship between diffusion tensor imaging (DTI) measures and the clinical status of severe traumatic brain injury (TBI) patients both at the time of MRI and their discharge to acute TBI rehabilitation and assess its prognostic value.

### **Methods**

Patients (n=79) admitted to the trauma center with severe closed head injury were retrospectively evaluated, after approval from the institution's IRB, to determine the prognostic value of DTI measures. The relationship of DTI measures including apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial ( $\lambda_{\parallel}$ ), and radial diffusivity ( $\lambda_{\perp}$ ) from the whole brain white matter, internal capsule, genu, splenium, and body of the corpus callosum were assessed with neurological status at MRI and at discharge to acute TBI rehabilitation.

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**Funding**

This work was partially supported by a grant from the DOD (Award # W81XWH-08-1-0725)



## **Introduction**

Traumatic Brain Injury (TBI) is a major cause of disability, morbidity, and mortality throughout the world. In the European Union, TBI resulting in death or hospitalization occurs at an approximate annual rate of 235 per 100,000, as well as hospital admission rates of 85 per 100,000 and emergency department visit rates of 403 per 100,000 annually in the United States (1). The estimated prevalence of individuals living with the neurological, neuropsychiatric, and cognitive sequelae of TB is between 2.5 to 6.5 million individuals in the United States alone (2). Due to its high incidence, debilitating consequences, and substantial social and economic costs, TBI is a disorder of major public health significance (2).

Consequences of TBI span across many domains of human function, with profound impact on the individual as well as their social and occupational function, and can potentially result in moderate to severe disability in up to half of the cases (2-3). Impairments in memory, attention, and executive function, in conjunction with neuropsychiatric sequelae, such as depression, anxiety, and personality changes, can be debilitating and adversely affect quality of life (2). Even individuals with normal-appearing conventional medical imaging can manifest TBI symptomatology (3).

Early in the course of TBI, prognosis can be complicated by the limitations of traditional clinical measures, such as the Glasgow Coma Scale (GCS) and computed tomography (CT). The GCS may fluctuate early after injury, and can be depressed by intoxication or medical intervention (intubation, sedation, or administration of paralytics) prior to admission or transfer (3; 5-7). Due to these factors, the European Brain Injury Consortium (EBIC) found that a full GCS was only testable in 56% of patients on admission to neurosurgical units (8). After admission, the GCS can decline due to evolving pathology over the first 72 hours post injury, and up to one third of patients who die of TBI will talk or obey commands before ultimately dying (3). Injury

classification systems based on CT findings, such as the Marshall score (9), are able to predict important clinical endpoints such as the risk of mortality or rising intracranial pressure (ICP), but qualitative scoring systems can suffer from significant inter-observer variability (3; 6). In the context of Traumatic Axonal Injury (TAI) or Diffuse Axonal Injury (DAI), patients can have normal-appearing CT and MRI early after the injury and still be profoundly comatose and have poor functional outcomes (10). Patients may also have a normal CT and neurological status depressed by intoxication (3; 6). Only ten percent of Traumatic Axonal Injury (TAI) cases will present with the typical hemorrhagic pattern on CT, and more than 80% of TAI is non-hemorrhagic, leading to an under-appreciation of axonal injury (3; 10). The diffuse nature of these injuries may not be apparent in the acute phase of injury on conventional diagnostic imaging, which may limit its prognostic value (10). Additionally, measures that are associated with survival may not necessarily be associated with good functional outcome as measured on the Glasgow Outcome Scale Extended (GOSE) (5).

There has been significant interest recently in the use of diffusion tensor imaging (DTI) in the evaluation of TBI patients. Diffusion MRI has shown sufficient sensitivity to visualize lesions which may be less conspicuous or absent on conventional MRI sequences (11), and thus may better depict diffuse injury in TBI (12). Since DTI is a quantitative, physiologically-derived parameter, it may provide a more objective measure of axonal injury for use in TBI classification and prognosis. Decreased fractional isotropy (FA) in the lobar white matter, corpus callosum, internal capsule, and other white matter structures has been reported in acute TBI patients (12-13), which appears to persist or evolve in the sub-acute and chronic phases of TBI (14-15). These decreases in FA have been linked to poor clinical outcomes or performance on cognitive testing in the chronic phases of injury (16-18). Although there are limited reports on the use of DTI among

severely injured TBI patients in the acute stage (19), the utility of DTI as a quantitative prognostic marker has not been established among severely injured patients.

The goal of this study was to determine whether DTI markers at admission, including axial diffusivity ( $\lambda_{\parallel}$ ), radial diffusivity ( $\lambda_{\perp}$ ), apparent diffusion coefficient (ADC), and FA at the whole-brain level and at the regional level provide prognostic information about the outcomes of severe TBI patients.

## **Methods**

The University of Maryland's institutional review board (IRB) approved this study for retrospective evaluation and was compliant with the requirements of the Health Insurance Portability and Accountability Act.

### *Patients*

Patients were selected and screened from a consecutive list of 126 individuals from the radiology database who received DTI as part of a standard clinical evaluation for blunt TBI on a 1.5 Tesla scanner between September 2007 and May 2009. Each patient's GCS was obtained at admission (admission GCS), from neurological and neurosurgical evaluations on the day of MRI (scan GCS), and at discharge (discharge GCS). Since the patient's GCS can be altered by intoxication, medical intervention prior to admission, or evolving TBI pathology, we used the minimum of the admission GCS and scan GCS (hereafter, minimum GCS) to determine if a patient's injury qualified as severe TBI. This allowed inclusion of patients whose GCS declined from the time of admission to the MRI scan, but did not include patients in the ranges of the GCS most prone to artificial depression by external factors. Patients who were admitted to the hospital with a moderate GCS (between 9 and 12) and remained at a moderate GCS level at the time of MRI were not included in this study for the reasons mentioned above. Of the 126 patients screened, 30 patients who had severe motion artifacts or image distortion on diffusion tensor

images were not included in this study. An additional 17 patients were not included because they did not meet the minimum age criteria or because their GCS was in the moderate range of 9-13. The total number of patients who ultimately were included in this study was 79, with 44 patients belonging to the severe TBI group and 35 patients belonging to the mild TBI reference group.

The total patient population ( $n=79$ , age= $38.5\pm17.7$ , range 18-94, 55 men, 24 women) that was included in the study consisted of a heterogeneous mixture of closed head injuries, from mechanisms including motor vehicle collisions ( $n=30$ ), falls ( $n=20$ ), struck pedestrians ( $n=9$ ), other vehicular accidents (bicycles, motorcycles, ATVs:  $n=8$ ), assaults ( $n=7$ ), or other mechanisms ( $n=5$ : found down (2), struck by large metal bar, sports injury, struck in the head by thrown object). Patients were imaged  $4.6\pm9.4$  days post admission (range of 57 days), with half of the sample imaged within one day of admission, and 75% imaged within five days of admission. The outcome for the severe TBI group ( $n=44$ , age  $37.9\pm17.2$  y; 36 male) was determined by discharge status from the hospital. Four outcome categories from the severe TBI group included death ( $n=10$ , age  $50.9\pm17.1$  y, 7 male, minimum GCS  $3.3\pm0.9$ ), or neurological status at the time of discharge to rehabilitation center: severe discharge GCS ( $n=8$ , age  $30.9\pm16$  y, 7 male, minimum GCS  $3.9\pm1.1$ ), moderate discharge GCS ( $n=18$ , age  $38.1\pm16.3$  y, 15 male, minimum GCS  $4.8\pm1.8$ ) or mild discharge GCS ( $n=8$ , age  $29.4\pm12.2$  y, 7 male, minimum GCS  $5.1\pm1.7$ ). All surviving severe TBI patients were discharged to rehabilitation between four and 50 days post-admission, with a median length of hospitalization of 20 days.

The mild TBI reference group consisted of 35 individuals (age  $36.84\pm16.9$  y, 18 male) who were all discharged from the hospital to home within  $5.0\pm7$  days and their GCS greater than 12 throughout their hospitalization. Example images of the patients belonging to each of the five outcome groups are shown in Figure 1.

### *MR Imaging*

All imaging was performed on a 1.5-T Avanto scanner (Siemens Medical Solutions; Erlangen, Germany) with parallel imaging capability. Conventional MR imaging included axial T2 using turbo spin echo ( $TE_{\text{eff}}/TR/ETL = 113/5,900 \text{ ms}/15$ , 5mm slices with 1mm inter-slice gap), FLAIR ( $TE_{\text{eff}}/TI/TR/ETL = 102/2,500/8,000/13 \text{ ms}$ , 5mm slices with 1mm inter-slice gap), T2\* ( $TE/TR = 30/500 \text{ ms}$  with  $25^\circ$  flip angle), volumetric T1 ( $TE/TR = 4.76/11 \text{ ms}$  with  $20^\circ$  flip angle,  $1\text{mm} \times 1\text{mm} \times 2\text{mm}$  voxels), and SWI ( $TE/TR = 40/50 \text{ ms}$  with  $25^\circ$  flip angle,  $0.5\text{mm} \times 0.5\text{mm} \times 2\text{mm}$  voxels).

DTI images were obtained using a double spin-echo echo-planar imaging technique over a 23cm FOV at a matrix size of  $128 \times 128$ , with contiguous 2mm thick slices (3 averages;  $TE/TR$  of  $95/11200\text{ms}$ , parallel imaging acceleration factor of 2). A total of 68 axial images were acquired to cover the brain from the apex to the skull base. Diffusion gradients were sensitized in 12 collinear directions at an effective b-value of  $1000 \text{ s/mm}^2$ .

### *Image Processing and Analysis*

The DTI images were exported offline and processed using FDT (FMRIB Diffusion Toolbox, FMRIB, Oxford, UK). Images were first corrected for eddy current induced image distortion following which the brain parenchyma was extracted using Brain Extraction Tool (BET) available within FSL (FMRIB Software Library, Oxford, UK), and the diffusion tensor was estimated for each voxel (Smith, 2002; Smith et al., 2004).

The FA maps of all patients were aligned to the ICBM template derived using data from 152 subjects and segmented into gray matter, white matter, and CSF maps using SPM5 (Wellcome Department of Imaging Sciences; University College London, UK). Segmented images were visually inspected to confirm accuracy of white matter segmentation results. The segmented white-matter images were used to obtain information on whole brain white matter ADC, FA, axial diffusivity ( $\lambda_{\parallel}$ ) and radial diffusivity ( $\lambda_{\perp}$ ) values. Regions of interest with varying

geometry to best fit the regions as shown in Figure 2 were drawn on the genu, splenium, and body of the corpus callosum and the internal capsule. Summary statistics such as the mean, standard deviation (SD), and coefficient of variation (CV) for each of the above parameters were calculated using MATLAB (Mathworks, Natick, MA). These summary measures were used in statistical models for prediction of patient's outcome category as described below.

### *Statistical Analysis*

Nonparametric correlation coefficients (Spearman's Partial Rho) adjusted for age and gender were used to examine the relationship in all patients between DTI parameters and the GCS at both time of MRI and at the time of discharge to TBI rehabilitation. Further, the relationship between each outcome category and DTI parameters on a global and regional level in the white matter in all patients was also examined.

Prognostic models of severe TBI patient outcomes were created using Ordinal Logistic Regression models. These models were adjusted for age, gender, time to scan, and admission GCS to determine if DTI parameters significantly improved prediction of patient outcome status among severe TBI patients. Improvement in model fit was judged by comparing the differences in model deviance to the critical values of the chi-square distribution. Regression models were chosen by best subset selection based on the score criterion, selecting from all whole brain DTI measures. Statistical analysis was conducted in SAS 9.2 for Windows XP (SAS Corporation, Cary, NC), and plots were produced using R (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance for all hypothesis testing procedures was judged at  $p < 0.05$ .

### **Results**

There was no difference in the median age between severe TBI patients and the mild TBI reference group. However, there were significant differences between the median ages of the different outcome groups ( $p = 0.016$ ). Bonferroni-adjusted post-hoc tests indicate that the median

ages significantly differed between severe TBI patients with mild GCS (age  $29.4 \pm 12.2$  y at discharge and severe TBI patients who died (age  $50.9 \pm 17.1$  y). No other groups differed significantly in median age.

### *Regional and Global DTI Correlation with GCS*

Table 1 lists the partial correlations between the DTI and scan GCS among all the patients included in this study. The average ADC ( $r=0.40$ ;  $p<0.0003$ ),  $\lambda_{\parallel}$  ( $r=0.57$ ;  $p<0.0001$ ) and  $\lambda_{\perp}$  ( $r=0.26$ ;  $p=0.019$ ) for the whole brain white matter demonstrated a strong positive relationship with scan GCS, indicating that global white matter decrements in DTI parameters are associated with poor outcomes from TBI. The CV of the above parameters, including those of FA, also demonstrated a significant negative correlation with scan GCS, suggesting that variability in the DTI values increased with the severity of the injury. Similar patterns of decrements in DTI parameters were observed for ADC ( $r=0.31$ ;  $p=0.06$ ) and  $\lambda_{\parallel}$  ( $r=0.64$ ;  $p<0.0001$ ) in the body of corpus callosum with the exception that average FA ( $r=0.46$ ;  $p<0.0001$ ) demonstrated a strong correlation with the scan GCS while no relationship of scan GCS with  $\lambda_{\perp}$  was observed at this location. The genu ( $r=0.54$ ;  $p<0.0001$ ), splenium ( $r=0.36$ ;  $p=0.001$ ) and the internal capsule ( $r=0.34$ ;  $p=0.0023$ ) demonstrated a strong correlation between  $\lambda_{\parallel}$  and the clinical status of the patient. The CV of axial diffusivity exhibited significant negative relationships with clinical status in every region except in the internal capsule.

### *DTI Parameters and Patient Outcomes*

Table 2 lists the average values of the various DTI parameters for each of the four patient outcome groups and the reference group for the whole brain white matter, internal capsule, genu, splenium and the body of the corpus callosum. At the whole brain white matter level, reduced average ADC and  $\lambda_{\parallel}$  were associated with poor patient outcomes at discharge while FA and  $\lambda_{\perp}$

were not significantly associated with patient outcomes. Regional measurements at the splenium, body of the corpus callosum, genu and the internal capsule exhibited similar relationships with patient outcomes, with the exception that the association of FA with patient outcomes was much stronger on a regional basis. The variability of the DTI values within the ROIs was also associated with patient status, with greater heterogeneity in the white matter being associated with poor patient outcomes.

The partial correlation coefficients between patient outcomes and DTI measures at the whole brain white matter and at the regional level for the patients who were considered severe based on GCS are listed in Table 3. Favorable patient outcomes were associated with higher mean ADC ( $r=0.257, p=0.023$ ) in the whole brain white matter as demonstrated in Figure 3. An even stronger relationship as observed between favorable patient outcomes and higher values of  $\lambda_{\parallel}$  ( $r=0.49, p<0.0001$ ) in the white matter, suggesting that the association between water diffusion changes and patient outcomes is primarily driven by changes in axial diffusivity. Greater heterogeneity in the DTI values, measured by the CV of ADC ( $r=-0.59, p<0.0001$ ) and  $\lambda_{\parallel}$  ( $r=-0.536, p<0.0001$ ) were strongly associated with poor patient outcomes. This association between the heterogeneity of the DTI values was also observed in FA ( $r=-0.308, p=0.006$ ) and  $\lambda_{\perp}$  ( $r=-0.48, p<0.0001$ ) although their mean values ( $r=0.177, p=0.12$  and  $r=0.103, p=0.37$  respectively) did not exhibit a strong relationship with patient outcome.

In the genu of the corpus callosum, lower averages of FA ( $r=0.318, p=0.004$ ), ADC ( $r=0.224, p=0.048$ ), and  $\lambda_{\parallel}$  ( $r=0.554, p<0.0001$ ) were significantly related to poor patient outcomes as shown in Figure 4. Additionally, higher CVs of FA ( $r=-0.275, p=0.015$ ) and  $\lambda_{\parallel}$  ( $r=-0.285, p<0.01$ ) were significantly related to poor patient outcomes. No relationship between  $\lambda_{\perp}$  ( $r<-0.07, p=0.54$ ) and outcome category was evident in the genu.



In the splenium of the corpus callosum, lower averages of FA ( $r=0.331, p=0.003$ ) and  $\lambda_{\parallel}$  ( $r=0.318, p=0.004$ ) were significantly related to poor patient outcomes as illustrated in Figure 5. Additionally, higher CVs of both FA ( $r=-0.361, p=0.001$ ) and  $\lambda_{\parallel}$  ( $r=-0.288, p=0.01$ ) were significantly related to poor patient outcomes. The relationship between ADC ( $r=0.049, p=0.66$ ) or  $\lambda_{\perp}$  ( $r=-0.174, p=0.128$ ) and outcome category was not significant.

Figure 6 shows a box plot of DTI parameters for the body of the corpus callosum, where higher average  $\lambda_{\perp}$  ( $r=-0.241, p=0.03$ ) and lower averages of FA ( $r=0.509, p<0.0001$ ) and  $\lambda_{\parallel}$  ( $r=0.555, p<0.0001$ ) were significantly related to poor patient outcomes. Additionally, higher CV of ADC ( $r=-0.325, p=0.003$ ), FA ( $r=-0.527, p<0.0001$ ), and  $\lambda_{\parallel}$  ( $r=-0.381, p=0.0006$ ) were significantly related to poor patient outcomes.

In the internal capsule, lower average  $\lambda_{\parallel}$  ( $r=0.27, p=0.017$ ) and higher CV of ADC ( $r=-0.42, p=0.02$ ) were significantly related to poor patient outcomes. There were trends between the average ( $r=0.205, p=0.073$ ) and CV ( $r=-0.222, p=0.053$ ) of FA and patient outcomes, with lower average FA and higher FA CV being related to poor patient outcomes.

### *Logistic Models for Patient Outcomes using DTI Parameters*

When predicting outcome using logistic models using one whole-brain DTI summary measure, the CV for whole brain white matter ADC and  $\lambda_{\parallel}$  best predicted outcome. The use of any whole-brain ADC or axial diffusivity measure (average, CV) significantly improved model prediction ( $p<0.05$ ), adjusted for admission GCS, age, gender, and time from admission to scan. Among the combinations of various DTI metrics, addition of  $\lambda_{\perp}$  had the least effect on model prediction while  $\lambda_{\parallel}$  and ADC had the strongest influence on model prediction. Due to the correlation between the various DTI measures at both the whole brain and regional level, little additional improvement in model fit was observed by adding more than three DTI measures.

## Discussion

Conventional CT and MR imaging provide valuable information for surgical planning in TBI patients, but are not adequate for the characterization, quantification, and determination of the extent of axonal injury (10). The GCS is a coarse neurological measure with known limitations in classifying the true extent of acute TBI, including reduced sensitivity in the lobar white matter, ceiling effects, and questions of reliability in the presence of intoxication or medical intervention prior to admission (3; 5-8). The results of our study suggest that parameters derived from DTI in the acute phase of severe injury are correlated with neurological status measured by the GCS, and provide prognostic information about a patient's future discharge status, independent of factors that may make GCS unreliable. These prognostic models were based only on severe TBI patients, indicating that DTI is sensitive enough to detect gradations of injury which are reflective of a patient's neurological status at discharge to acute rehabilitation, and these relationships persist even after adjusting for two of the strongest prognostic indicators of functional outcome and mortality (5). Poor clinical outcomes were associated with acute, global reductions in the averages of both  $\lambda_{\parallel}$  and ADC. While the association between global white matter FA averages and clinical outcomes did not reach statistical significance, the CV did exhibit a strong association with clinical outcomes. The CV appears to be a powerful and sensitive summary measure of DTI alterations in TBI.

Investigation of ADC as a trauma biomarker have been mixed, with trauma being associated with increased ADC (14-15), decreased ADC (13), or no change in ADC relative to controls (12). This heterogeneity may be due to differences in the anatomical regions sampled, quantitative methodological differences, or temporal trends in ADC following TBI, which have been exhibited in animal studies (20).

In our study, the association between the average FA of the whole brain white matter and discharge neurological status did not reach statistical significance. However, regional FA measures in the corpus callosum and internal capsule demonstrated greater sensitivity. In the corpus callosum, average axial diffusivity and average FA were significantly related to clinical outcomes, with worse outcomes associated with increasing decrements in these parameters. The relationship between decreased FA and trauma severity in several regions of the brain including the corpus callosum is reiterated by several other investigations of TBI, irrespective of injury severity and the time since injury (13-15; 18; 21-26) suggesting that changes in the fractional anisotropy within the corpus callosum to be both a sensitive and stable marker of injury in TBI. Some investigators found relationships between changes in FA and outcome status in severe TBI patients (14; 18; 21; 26), while at least one study found no association between FA changes and either the post-resuscitation GCS or the GOS (19).

Controlled cortical impact (CCI) animal models of TBI help elucidate the pathological mechanisms underlying DTI changes. Mac Donald and colleagues (20) observed acute and subacute (four hours to four days post-injury) reductions in ADC, FA, and axial diffusivity in the cortex ipsilateral and contralateral to the lesion which were associated with primary axonal injury. Subacute (one week to one month post-injury) increases in ADC and axial diffusivity were associated with edema, demyelination, and gliosis. Since the majority of our study group was imaged within five days of injury (acute to sub-acute stage), it is likely that our findings of reduced axial diffusivity are reflective of a combination of primary axonal injury and the early effects of secondary injury (20) and that the extent of this axonal injury could be predictive of patient outcome. Development of accurate diagnostic and prognostic markers in TBI is an important step in developing effective treatment and rehabilitation strategies (1-2; 5-6). Diffusion Tensor MRI appears to provide several biomarkers that relate to the patho-physiological

conditions of the white matter, which are correlated with existing clinical measures, yet provides more information about a patient's discharge status. DTI has also been shown to detect abnormalities which are not visualized or appreciated on conventional imaging. The quantitative protocol used in this study could be easily translated to the clinical workflow, and regional measures can help extend the usefulness of DTI to patients whose injuries prohibit the use of whole-brain segmentation algorithms to separate gray and white matter. The usefulness of these DTI parameters as a prognostic marker needs to be further extended to longitudinal studies relating DTI findings to long term biological, psychological, and social outcomes.

DTI estimation benefits from a larger number of diffusion-sensitizing gradient directions (27), and future prospective evaluations of DTI as a prognostic marker in TBI should take advantage of the latest techniques available. Since our patients were retrospectively evaluated in the acute setting at discharge to TBI rehabilitation, rehabilitation outcome measures such as the GOS were not available (28). While the GCS on admission to rehabilitation is associated with functional recovery (29-30), further research is necessary to associate acute DTI with long-term functional outcome. Without established scoring criteria for MRI, analogous to the Marshall Score for CT (9), it is difficult to compare the prognostic value of DTI to conventional imaging. While our study involved only patients with a head injury, future studies should involve healthy volunteers to determine an absolute scale between normal human variability and the range of DTI values seen across the spectrum of TBI. Our study investigated severe TBI patients in the acute setting, who are under-represented in the literature. Patients were evaluated with DTI early in the course of injury using a simple whole-brain and ROI methodology which could be readily translated for clinical use. Prognostic models showed that axial diffusivity and FA provided prognostic information about patient outcomes in severe TBI, which likely reflects the degree of

underlying axonal injury. The CV of these DTI measures is a powerful summary measure, capturing both decreases in mean values and increases in variance within ROIs.

## **Conclusion**

Our study demonstrated that DTI parameters at the whole brain level and regional level can provide prognostic information about the discharge status of a patient while circumventing many problems associated with currently used clinical measures, including the GCS. The relationship between DTI and discharge neurological status remained significant even after adjusting for two of the strongest prognostic factors in TBI. Axial diffusivity appears to provide the most prognostic information about outcome status, on both regional and global scales. The CV captures information about both the mean and the variability in the data, making it a parsimonious summary measure for DTI values. While these results are promising, prospective longitudinal studies are necessary to validate these findings.

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**Table 1.** Partial correlations between DTI parameters and Glasgow Coma Scale on the day of MRI in all patients for global and regional white matter volumes, adjusted for age and gender. The internal capsule could not be measured in one patient due to the severity of her injuries preventing ROI placement. The p-values are provided in parenthesis for each of the correlations. Significant correlations are shown in bold.

	<b>FA Avg</b>	<b>FA CV</b>	<b>ADC Avg</b>	<b>ADC CV</b>	<b><math>\lambda_{\parallel}</math> Avg</b>	<b><math>\lambda_{\parallel}</math> CV</b>	<b><math>\lambda_{\perp}</math> Avg</b>	<b><math>\lambda_{\perp}</math> CV</b>
<b>Whole Brain White Matter</b>	0.014 (0.90)	<b>-0.286</b> <b>(0.011)</b>	<b>0.403</b> <b>(0.0003)</b>	<b>-0.531</b> <b>(&lt;0.0001)</b>	<b>0.575</b> <b>(&lt;0.0001)</b>	<b>-0.448</b> <b>(&lt;0.0001)</b>	<b>0.266</b> <b>(0.019)</b>	<b>-0.432</b> <b>(&lt;0.0001)</b>
<b>Genu of Corpus Callosum</b>	0.167 (0.14)	-0.10 (0.38)	<b>0.280</b> <b>(0.014)</b>	-0.192 (0.09)	<b>0.539</b> <b>(&lt;0.0001)</b>	<b>-0.274</b> <b>(0.016)</b>	0.046 (0.69)	0.015 (0.89)
<b>Body of Corpus Callosum</b>	<b>0.457</b> <b>(&lt;0.0001)</b>	<b>-0.479</b> <b>(&lt;0.0001)</b>	<b>0.307</b> <b>(0.006)</b>	<b>-0.311</b> <b>(0.0059)</b>	<b>0.638</b> <b>(&lt;0.0001)</b>	<b>-0.381</b> <b>(0.0006)</b>	-0.134 (0.24)	-0.089 (0.44)
<b>Splenium of Corpus Callosum</b>	0.170 (.14)	<b>-0.276</b> <b>(0.015)</b>	0.173 (0.13)	-0.183 (0.11)	<b>0.365</b> <b>(0.0011)</b>	<b>-0.321</b> <b>(0.0045)</b>	-0.026 (0.82)	0.001 (0.99)
<b>Internal Capsule</b>	<b>0.258</b> <b>(0.0242)</b>	-0.158 (0.172)	0.038 (0.744)	<b>-0.498</b> <b>(&lt;0.0001)</b>	<b>0.344</b> <b>(0.0023)</b>	-0.186 (0.10)	-0.168 (0.146)	-0.190 (0.1)

**Table 2.** Values of DTI parameters for the five categories of patients from the whole brain white matter, genu, body of the corpus callosum, splenium, and the internal capsule.

	<b>Whole Brain White Matter</b>			
<b>Outcome Category</b>	<b>ADC Avg, *10<sup>-3</sup> mm<sup>2</sup>/s</b>	<b>FA Avg</b>	<b><math>\lambda_{\parallel}</math> Avg, *10<sup>-3</sup> mm<sup>2</sup>/s</b>	<b><math>\lambda_{\perp}</math> Avg, *10<sup>-3</sup> mm<sup>2</sup>/s</b>
<b>Dead (n=10)</b>	0.68 ± 0.15	0.41 ± 0.05	0.97 ± 0.19	0.53 ± 0.13
<b>Severe (n=8)</b>	0.69 ± 0.05	0.41 ± 0.03	0.99 ± 0.05	0.53 ± 0.04
<b>Moderate (n=18)</b>	0.71 ± 0.04	0.42 ± 0.03	1.05 ± 0.05	0.55 ± 0.04
<b>Mild (n=8)</b>	0.75 ± 0.02	0.40 ± 0.02	1.09 ± 0.03	0.58 ± 0.03
<b>Control (n=35)</b>	0.73 ± 0.02	0.42 ± 0.02	1.08 ± 0.03	0.55 ± 0.02
	<b>Genu of Corpus Callosum</b>			
<b>Dead (n=10)</b>	0.67 ± 0.18	0.66 ± 0.11	1.23 ± 0.27	0.39 ± 0.16
<b>Severe (n=8)</b>	0.64 ± 0.08	0.61 ± 0.08	1.14 ± 0.22	0.38 ± 0.0
<b>Moderate (n=18)</b>	0.65 ± 0.10	0.71 ± 0.07	1.28 ± 0.17	0.33 ± 0.09
<b>Mild (n=8)</b>	0.73 ± 0.06	0.66 ± 0.08	1.39 ± 0.12	0.41 ± 0.08
<b>Control (n=35)</b>	0.71 ± 0.07	0.72 ± 0.07	1.42 ± 0.09	0.35 ± 0.08
	<b>Body of Corpus Callosum</b>			
<b>Dead (n=10)</b>	0.70 ± 0.21	0.66 ± 0.10	1.33 ± 0.34	0.39 ± 0.17
<b>Severe (n=8)</b>	0.66 ± 0.12	0.63 ± 0.10	1.20 ± 0.21	0.39 ± 0.11
<b>Moderate (n=18)</b>	0.76 ± 0.08	0.67 ± 0.05	1.45 ± 0.14	0.41 ± 0.07
<b>Mild (n=8)</b>	0.76 ± 0.05	0.69 ± 0.05	1.49 ± 0.09	0.40 ± 0.06
<b>Control (n=35)</b>	0.76 ± 0.04	0.73 ± 0.04	1.56 ± 0.09	0.36 ± 0.05
	<b>Splenium of Corpus Callosum</b>			
<b>Dead (n=10)</b>	0.67 ± 0.25	0.69 ± 0.16	1.29 ± 0.38	0.37 ± 0.23
<b>Severe (n=8)</b>	0.73 ± 0.13	0.64 ± 0.09	1.34 ± 0.21	0.42 ± 0.12
<b>Moderate (n=18)</b>	0.68 ± 0.11	0.75 ± 0.09	1.41 ± 0.15	0.31 ± 0.12
<b>Mild (n=8)</b>	0.77 ± 0.06	0.70 ± 0.06	1.52 ± 0.10	0.39 ± 0.08
<b>Control (n=35)</b>	0.71 ± 0.06	0.76 ± 0.06	1.51 ± 0.11	0.32 ± 0.07
	<b>Internal Capsule</b>			
<b>Dead (n=10)</b>	0.65 ± 0.12	0.57 ± 0.11	1.11 ± 0.13	0.42 ± 0.13
<b>Severe (n=8)</b>	0.62 ± 0.09	0.56 ± 0.06	1.05 ± 0.16	0.41 ± 0.07
<b>Moderate (n=18)</b>	0.70 ± 0.06	0.55 ± 0.07	1.17 ± 0.10	0.46 ± 0.07
<b>Mild (n=8)</b>	0.70 ± 0.03	0.57 ± 0.05	1.19 ± 0.06	0.45 ± 0.04
<b>Control (n=35)</b>	0.68 ± 0.03	0.60 ± 0.05	1.20 ± 0.06	0.41 ± 0.04

**Table 3.** Partial correlations between DTI parameters and outcome category in all patients for global and regional white matter volumes, adjusted for age and gender. The internal capsule could not be measured in one patient due to the severity of her injuries preventing ROI placement. The p-values are provided in parenthesis for each of the correlations. Significant correlations are shown in bold.

	<b>FA Avg</b>	<b>FA CV</b>	<b>ADC Avg</b>	<b>ADC CV</b>	<b><math>\lambda_{\parallel}</math> Avg</b>	<b><math>\lambda_{\parallel}</math> CV</b>	<b><math>\lambda_{\perp}</math> Avg</b>	<b><math>\lambda_{\perp}</math> CV</b>
<b>Whole-Brain White Matter</b>	0.177 (0.12)	<b>-0.308</b> <b>(0.006)</b>	<b>0.257</b> <b>(0.023)</b>	<b>-0.599</b> <b>(&lt;0.0001)</b>	<b>0.491</b> <b>(&lt;0.0001)</b>	<b>-0.537</b> <b>(&lt;0.0001)</b>	0.103 (0.37)	<b>-0.489</b> <b>(&lt;0.0001)</b>
<b>Genu of Corpus Callosum</b>	<b>0.318</b> <b>(0.004)</b>	<b>-0.275</b> <b>(0.015)</b>	<b>0.224</b> <b>(0.048)</b>	-0.189 (0.097)	<b>0.554</b> <b>(0.0001)</b>	<b>-0.285</b> <b>(0.011)</b>	-0.070 (0.54)	0.107 (0.34)
<b>Body of Corpus Callosum</b>	<b>0.509</b> <b>(0.0001)</b>	<b>-0.527</b> <b>(0.0001)</b>	0.202 (0.075)	<b>-0.325</b> <b>(0.0037)</b>	<b>0.555</b> <b>(0.0001)</b>	<b>-0.381</b> <b>(0.0006)</b>	<b>-0.241</b> <b>(0.033)</b>	-0.066 (0.56)
<b>Splenium of Corpus Callosum</b>	<b>0.331</b> <b>(0.003)</b>	<b>-0.361</b> <b>(0.001)</b>	0.049 (0.66)	-0.122 (0.28)	<b>0.318</b> <b>(0.0045)</b>	<b>-0.288</b> <b>(0.01)</b>	-0.174 (0.128)	0.138 (0.22)
<b>Internal Capsule</b>	0.205 (0.073)	-0.222 (0.053)	-0.021 (0.86)	<b>-0.420</b> <b>(0.0001)</b>	<b>0.270</b> <b>(0.017)</b>	-0.130 (0.2584)	-0.149 (0.195)	-0.196 (0.088)

## Figure Legends

Figure 1. Exemplary conventional images (T1-MPRAGE/FLAIR/SWI) for each outcome group, Column (a) Example of a severe TBI patient imaged within a day of admission and presented with multiple hemorrhagic contusions resulting in death the following day, (b) patient with right craniectomy with external herniation of brain, extensive contusions, subdural hematoma, and edema following pole-vaulting accident was discharged with a severe GCS of 7T after 43 days in hospital, (c) patient involved in motor vehicle collision with multiple hemorrhagic contusions and evidence of hemorrhage in the gray matter consistent with diffuse axonal injury discharged with a moderate GCS of 11T after spending 19 days in the hospital, (d) patient struck by a car with diffuse axonal shear injury in the left external capsule was discharged from the hospital after one week with a mild GCS of 14, and (e) patient belonging to the control group who had an altered level of consciousness after being involved in motor vehicle accident admitted with a mild GCS of 15 and discharged from the hospital within two days.

Figure 2. Example of typical ROI's in the internal capsule (blue), genu (green), splenium (red) and body of the corpus callosum (orange) from where the DTI parameters were obtained.

Figure 3. DTI parameters including average MD, FA, and  $\lambda_{\parallel}$  and their coefficient of variation (CV) for the whole brain white matter for the different outcome groups.

Figure 4. DTI parameters including average MD, FA, and  $\lambda_{\parallel}$  and their coefficient of variation (CV) for the genu of the corpus callosum for the different outcome groups.

Figure 5. DTI parameters including average MD, FA, and  $\lambda_{\parallel}$  and their coefficient of variation (CV) for the splenium of the corpus callosum for the different outcome groups.

Figure 6. DTI parameters including average MD, FA, and  $\lambda_{\parallel}$  and their coefficient of variation (CV) for the body of the corpus callosum for the different outcome groups.



Figure 1  
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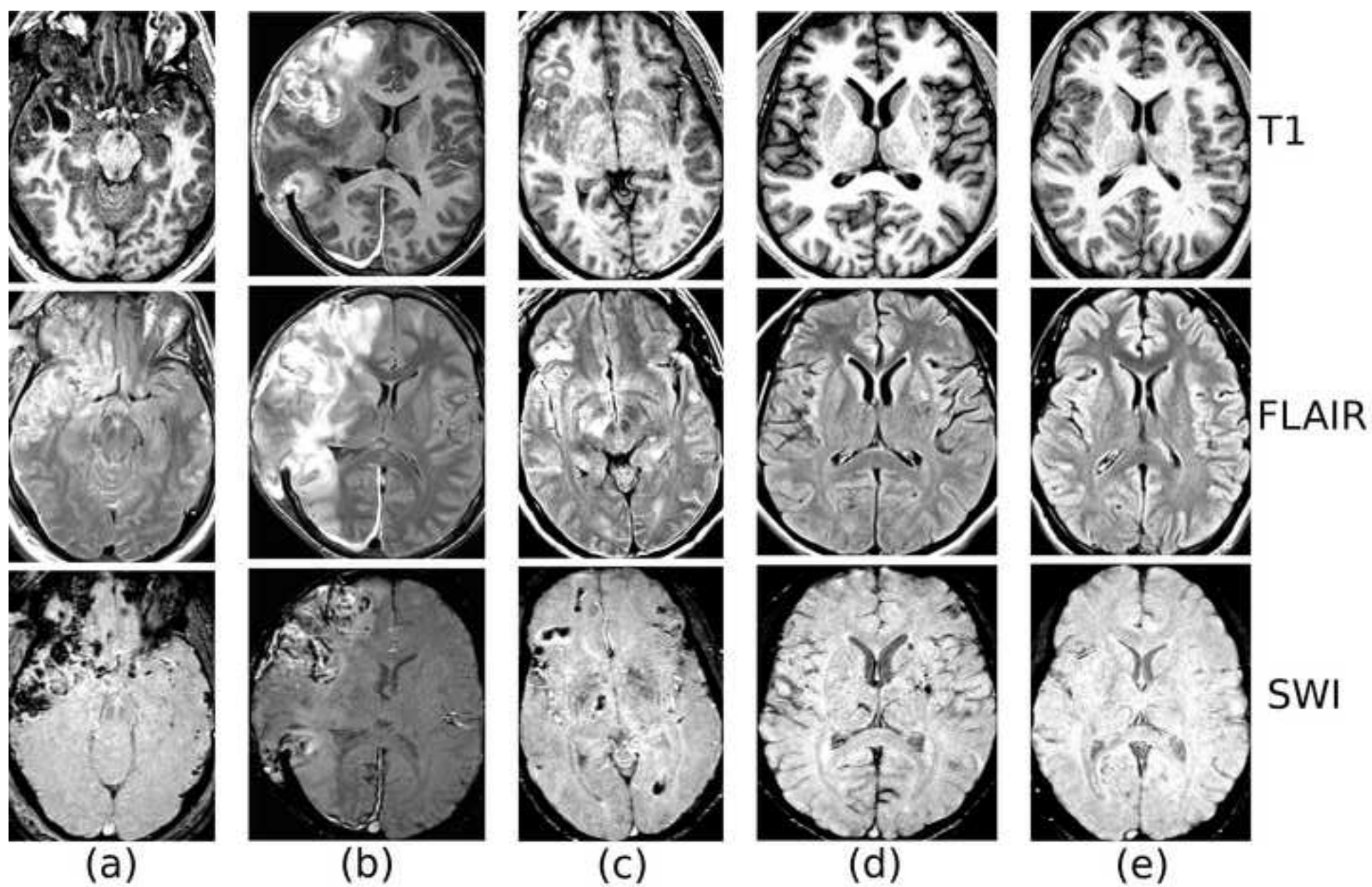
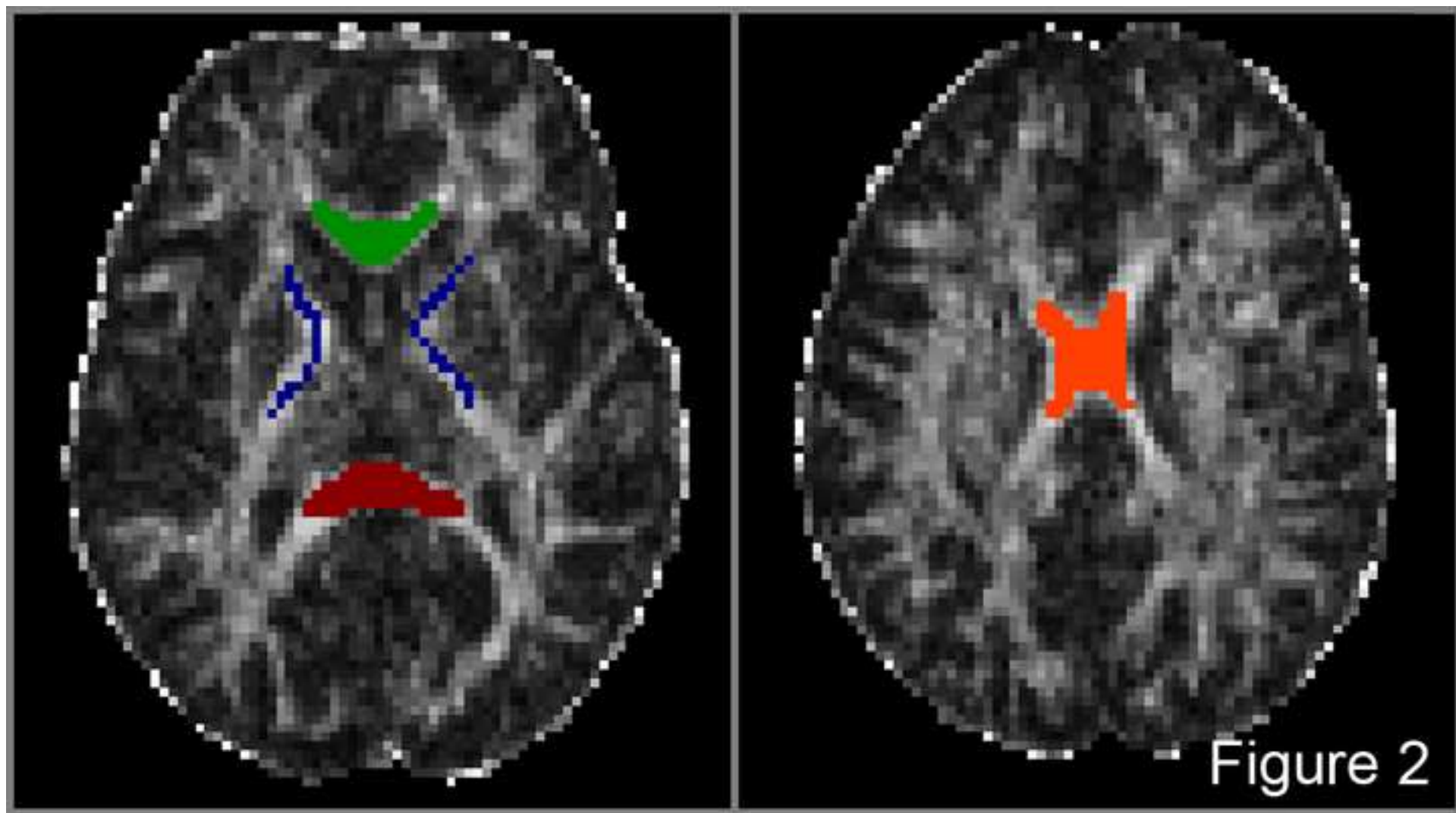


Figure 1

Figure 2  
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**Figure 3**  
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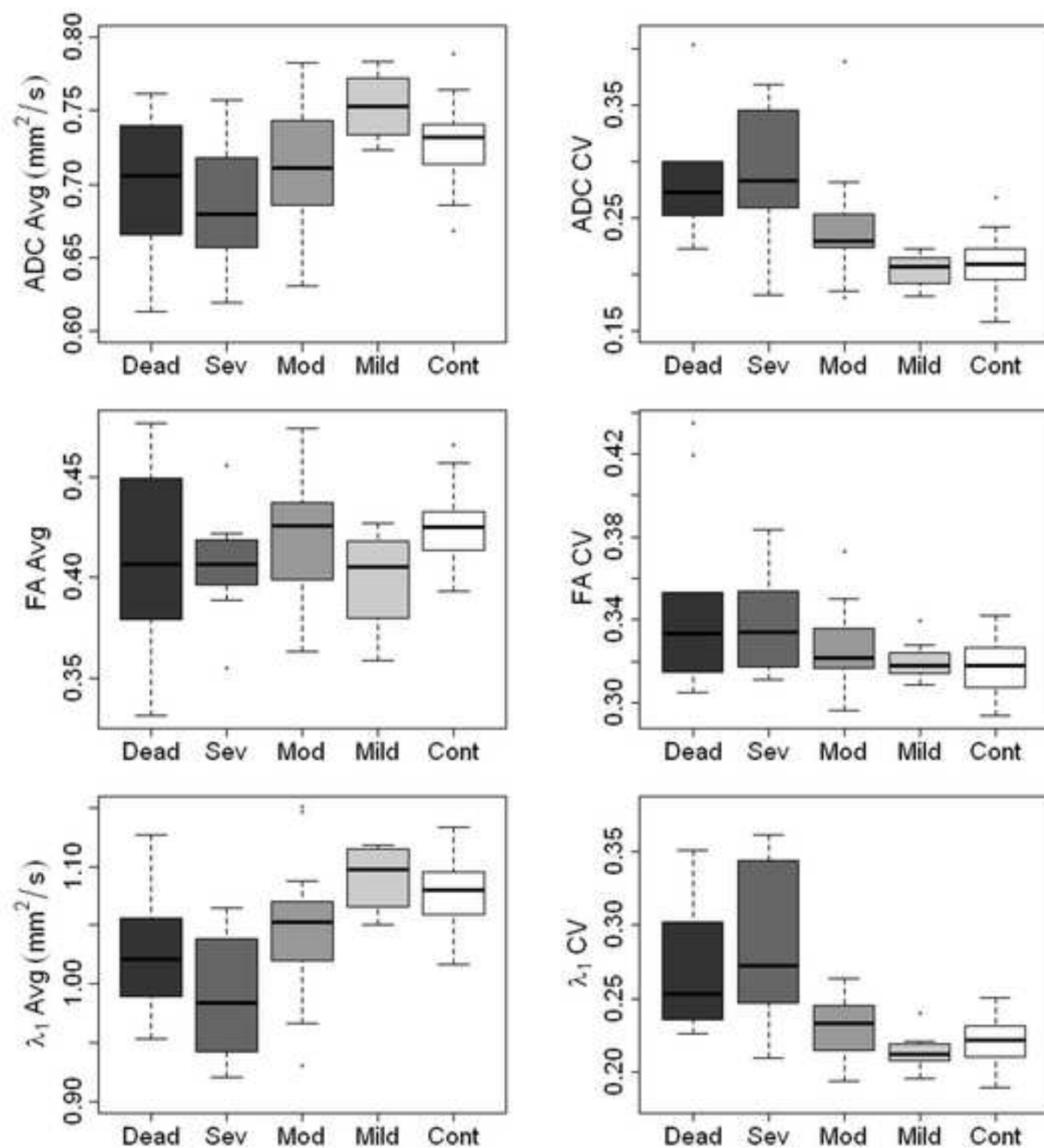
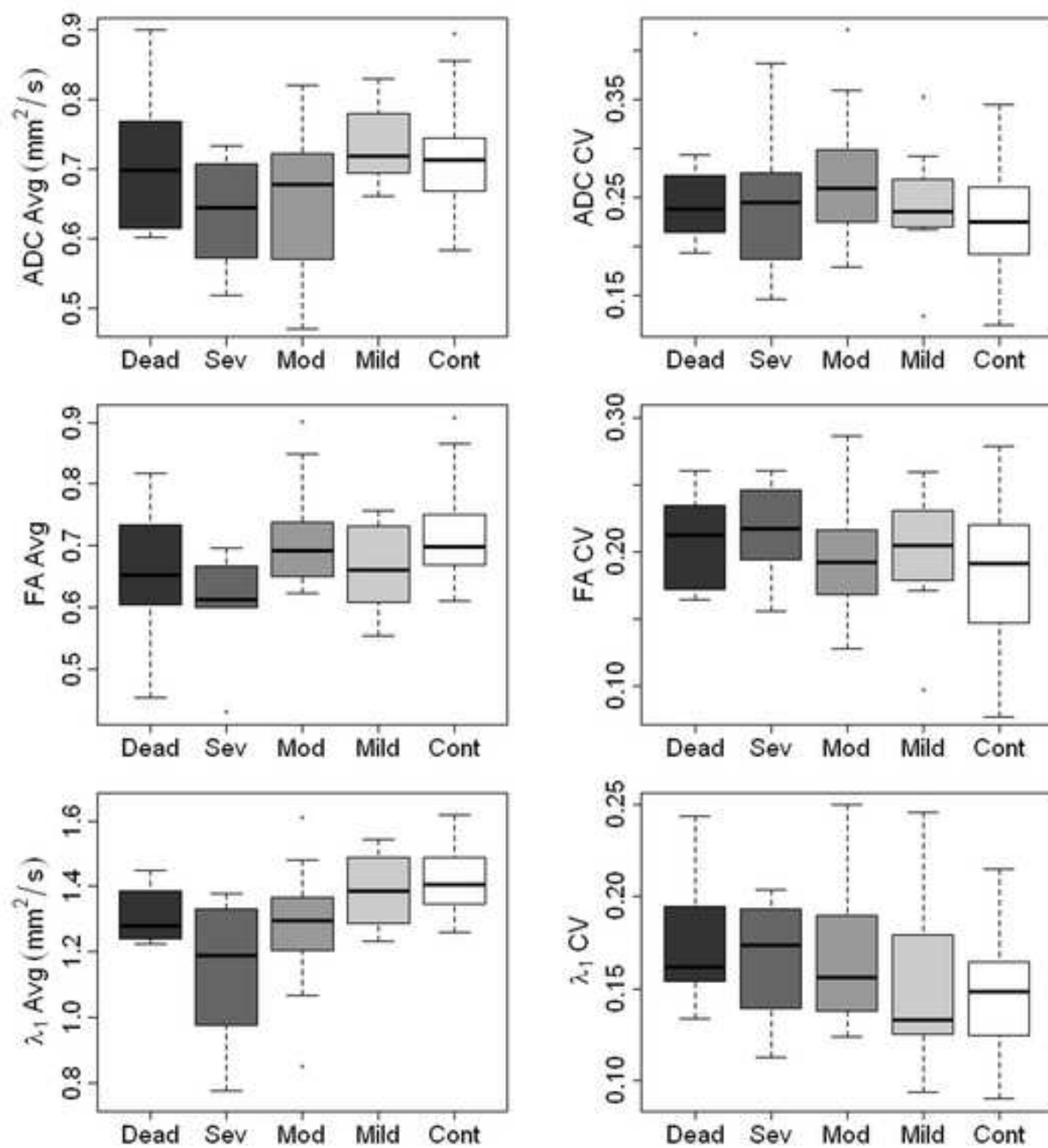
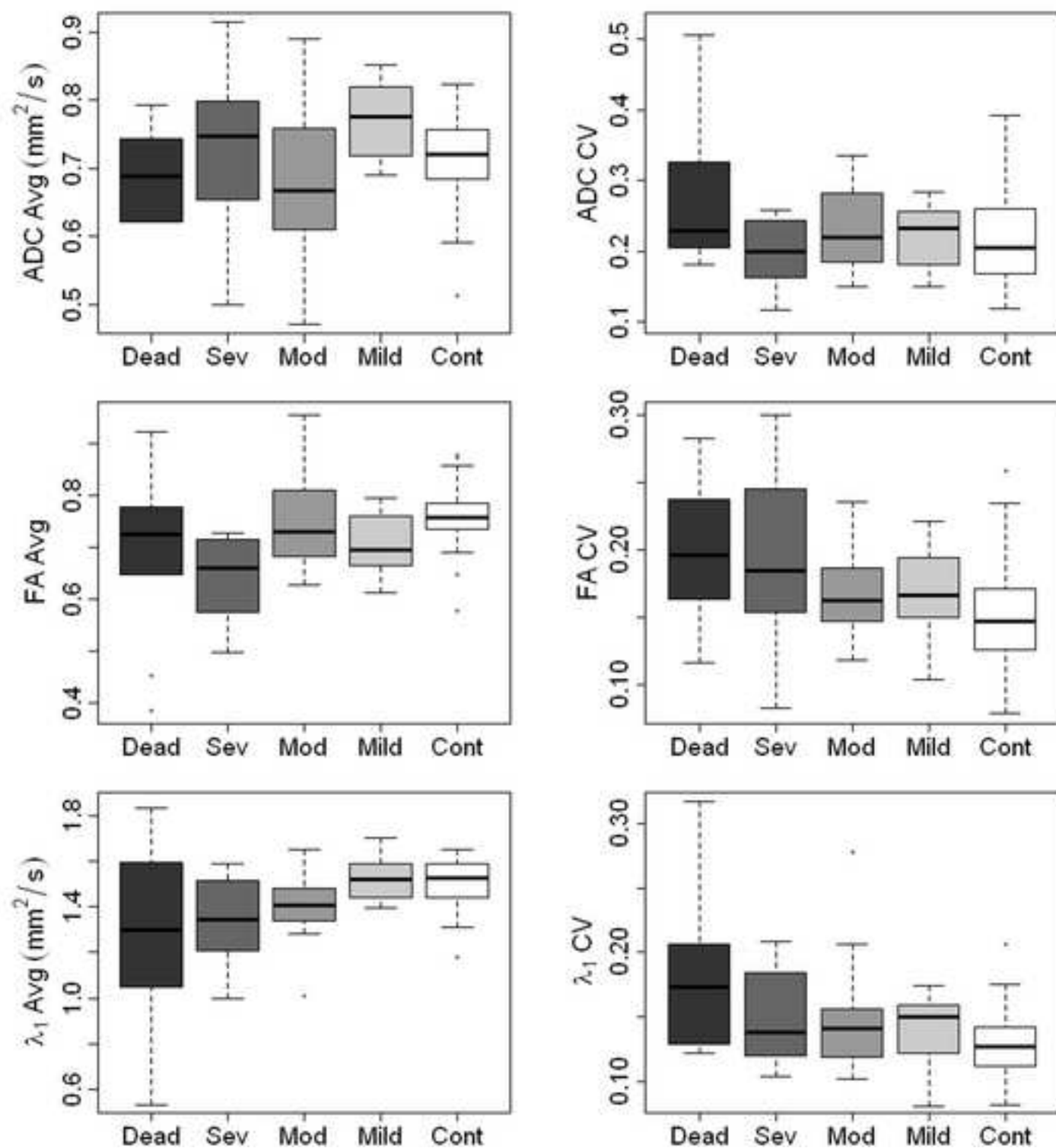


Figure 4  
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**Figure 5**  
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**Figure 6**  
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